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Male risk taking, female odors, and the role of estrogen receptors

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ABSTRACT

Male risk-taking and decision making are affected by sex-related cues, with men making riskier choices and decisions after exposure to either women or stimuli associated with women. In non-human species females and, or their cues can also increase male risk taking. Under the ecologically relevant condition of predation threat, brief exposure of male mice to the odors of a sexually receptive novel female reduces the avoidance of, and aversive responses to, a predator. We briefly review evidence showing that estrogen receptors (ERs), ERα and ERβ, are associated with the mediation of these risk taking responses. We show that ERs influence the production of the female odors that affect male risk taking, with the odors of wild type (ERαWT, ERβWT), oxytocin (OT) wildtype (OTWT), gene-deleted 'knock-out' ERβ (ERβKO), but not ERαKO or oxytocin (OT) OTKO or ovariectomized (OVX) female mice reducing the avoidance responses of male mice to cat odor. We further show that administration of specific ERα and ERβ agonists to OVX females results in their odors increasing male risk taking and boldness towards a predator. We also review evidence that ERs are involved in the mediation of the responses of males to female cues, with ERα being associated with the sexual and both ERβ and ERα with the sexual and social mechanisms underlying the effects of female cues on male risk taking. The implications and relations of these findings with rodents to ERs and the regulation of human risk taking are briefly considered.

1. Introduction

What factors guide an individual's decisions when faced with potential risk? A growing body of evidence suggests that decisions regarding risk and risk taking in males are affected by sexual cues and stimuli. Men are reported to make "poorer" and "riskier" decisions when female related cues or stimuli are present (e.g. [1–4]). These decisions are suggested to facilitate sexually motivated behaviors with men's time perspective being shifted away from the long term consequences of their choices and focused on the immediate that is associated with the availability of a possible sexual partner [1,3,6]. Likewise in non-human species the presence of, either a female or sexual stimuli associated with a female, increases male risk taking in ecologically relevant contexts. For example, in rodents where chemical signals play a key role in social communication, male mice that are exposed to female odor show reduced fear responses and greater risk taking. Brief exposure to the odors of a novel sexually receptive female enhances the risk taking and boldness displayed by male mice towards a predator [7,8].

There is also an expanding interest in the neurobiological mechanisms that underlie social and sexual behaviors and responses [9–12]. Sex steroid hormones are excellent candidates for mediating external and internal information into adaptive behavioral responses to various challenges and opportunities (i.e. mating). There is substantial evidence suggesting that estrogens and estrogen receptors (ERs) have an important role in determining various aspects of social and sexual behavior in males as well in females [11,12] and are likely involved in the mediation of sexually associated risk taking [8]. Here, we first briefly review the effects of female cues on male risk taking, focusing on: (i) the effects of female sexual cues and stimuli on male risk taking in humans and other species and; (ii) the specific effects of exposure to female odors on the responses of male mice to predator threat. Secondly, we consider: (iii) the roles of estrogen receptors (ERα and ERβ) in risk taking, specifically reporting the results of studies showing the involvement of ERα and ERβ in the expression of female odors that influence socio-sexual responses and risk taking in male mice; and finally, (iv) we review the roles of ERs in mediating the risk taking responses elicited in males by exposure to female odor cues.

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2. Sexual cues and male risk taking

Sex-related cues have a significant impact on male behavior. A growing body of literature suggests that sexual motivation and augmented arousal elicited by females or their cues leads males to make riskier decisions and choices (e.g. [3,6,13]). This may be due to a decline and, or shift in men's cognitive performance. For example, men's cognitive performance, as assessed by a working memory task involving word lists, is reduced and more impulsive after a short interaction with a woman, especially if that woman is attractive [14]. Brief exposure of men to photos and videos of women engaged in sexual activity has also been associated with poorer performance on a cognitive go/no-go task [15]. Moreover, there is evidence suggesting that just the mere anticipation of an interaction with a woman that might be an attractive sexual partner and potential mate can reduce men's cognitive performance (Stroop color naming task), leading to riskier and poorer decisions [16].

Face-to-face contact with a fertile woman leads to greater risk taking by men in a gambling scenario [17]. Exposure to sexual photos of women has also been shown to enhance risk taking by men in a monetary reward context [3]. Likewise exposure to erotic images of women leads to men taking riskier economic and financial decisions [14]. However, it should be noted that in the economic and finance literature risk seeking and taking is usually defined in terms of a preference for a higher-variance pay off, whereas clinical and other researchers generally identify risk taking in terms of behaviors that can result in loss or harm to oneself or others. The latter may better capture the ambiguous nature of "real world" risky decision making in which choices are often associated with both rewards and risks of adverse consequences, which may be physically unrelated to one another. For a review of various measures of economic risk taking and their relations to other measures of risk taking see Schonberg et al. [18].

Results of several studies have revealed that the presence of an attractive woman can enhance immediate physical risk taking in young men (e.g. skate-boarding [19], crossing a road in the face of traffic [20], and in a virtual reality scenario crossing an ominous bridge [21]). Riskier sexually related decisions are also evident after exposure to female cues and images [22]. Ariely and Lowenstein [4] found that male heterosexual undergraduate students made a series of riskier judgments and decisions, including several related to HIV-related sexual risk, when sexually motivated and aroused after viewing sexual cartoons as compared to when not aroused (for discussions of the relationship between sexual motivation and arousal see [23–26]).

The enhanced risk taking elicited in men by sexually related cues has in several studies been associated with testosterone [2,27,28]. Slight rises in cortisol, possibly associated with arousal, have also been reported to occur in men and suggested to play a role in human mate responses, though larger rises likely suppress sexual functioning [2,27]. Sexual and erotic thoughts and psychological sexual arousal have been indicated to increase testosterone in men as well as in women [29]. In a classic study, Anonymous [30] reported that his beard growth, a bioassay for testosterone, increased on the days prior to sexual activity with his partner, perhaps due to the anticipation of sex.

Rapid (20–40 min) rises in salivary testosterone and physical risk taking have been documented in young men after non-sexual social interactions with attractive young women [2,19,27]. It is suggested that these rises in testosterone may focus attention on rewards and reduce sensitivity to losses, both of which are likely to enhance risky decision making [31] and likely, also affect economic decision making [9]. It was also found that larger testosterone increases in response to possible interactions with women were seen among men with smaller numbers of CAG codon repeats in exon 1 of the androgen receptor which are associated with a greater expression of the androgen receptor [32,33]. In this regard, the 2D:4D digit ratio, which has been considered as a proxy of prenatal testosterone exposure and possibly influences adult testosterone sensitivity, was also shown to influence the impact of sexual images on men's decisions [5]. There were, however, in most cases substantial inter- and intra-individual variation in these single acute measures of male testosterone levels.

Administration for 7 days of the aromatase (estrogen synthase) inhibitor, letrozole, which reduces the transformation of testosterone into estrogens such as 17β-estradiol, and resulted in elevated levels of testosterone (high end of normal levels), also led to men making riskier decisions under conditions of unknown probabilities (balloon analog risk task) but not in conditions of known probabilities (game of dice task) or when strategic decision making was required (Iowa gambling task with an incremental increase in decision probability) [34]. This was, in part, consistent with the positive correlation of daily natural testosterone levels with risk taking in economic decisions by financial day traders [35], though this was not found in a subsequent study examining the effects of testosterone administration in post-menopausal women [36]. It should be noted that none of the tasks in the aromatase studies involved sexual cues and sexually related decisions. However, importantly, it was suggested that the effects of testosterone on risk taking may also be related to, and, incorporate simultaneous variations in the metabolite of testosterone, estradiol. As subsequently discussed there is evidence that estrogen receptors are involved in the mediation of the effects of exposure to female cues on naturalistic risk taking by male rodents [7,8]. Testosterone could either directly, or indirectly, through aromatization to estradiol and subsequent effects on estrogen receptors, along with modifications in other neurochemical systems (e.g. serotonin, dopamine, glutamate, neuroactive steroid metabolites), affect cognition and anxiety leading to changes in risk taking (e.g. [10–12,37–39]).

This link between exposure to sexual stimuli and increases in testosterone is found in a variety of other non-human species of vertebrates. For example, sexual stimuli have been shown to trigger a rapid (less than 45 min) release of testosterone in male mice and rats (e.g., [37,39–45]), with novel females having particularly potent effects [46]. Sexual behavior per se is not needed for these responses to occur as increases in testosterone are evident in males after exposure to sexually receptive females placed behind transparent barriers (e.g. [37,43]) or to female chemosensory stimuli such as urine or vaginal secretions (e.g. [7,39,43,44,46]).

3. Predator exposure and male risk taking

In non-humans, predation threat has provided an ethologically relevant means for examining risk taking and decision making [47,48]. Anti-predator response patterns are shaped by tradeoffs between the benefits associated with the successful detection and avoidance of predation threat and those associated with a suite of fitness-related response patterns such as foraging, territorial defense, and mating. Results of studies with guppies and other species of fish have provided evidence indicating that the presence of a female is directly associated with a greater risk taking, increasing male boldness in the presence of predators [49]. The behavioral changes evident in males either after exposure to, or in the presence of, a female may involve an overall reduced fearfulness that leads to enhanced responses to potential mating opportunities.

Animals usually respond to the threat of predation risk with a number of defensive behaviors including either immobilization or fleeing and risk assessment (e.g. decision making as to when and how to forage, etc. in the presence of a predator), increased vigilance, and the suppression of non-defensive behaviors [48,50–53]. Results of field, laboratory, and semi-natural studies have shown that rodents display aversive and avoidance responses to either predators, or the odors of predators such as the domestic cat [48]. As found in prior

investigations [7,8] and shown in Fig. 1 when male mice were given a choice in an odor preference test between predator (cat) and non predator odor (almond) they displayed an intense aversion to, and avoidance of, cat odor. Preference here implies actively going to and inspecting/approaching the threatening stimulus and provides a measure of risk taking and boldness. This predator avoidance involves a heightened anxiety and fearfulness that is sensitive to anxiolytic agents (e.g. [51,53]).

An additional consequence of exposure to either a predator or predator odors is a reduction in nociceptive sensitivity and the induction of antinociception or analgesia. Mice and other rodents display pronounced analgesic responses (as measured by either the latency of foot-lifting responses to a warm surface or tail flick response) following brief exposure to predators or odors of specific predators such as a cat (e.g. [7,54,55] and Fig. 2). This analgesia is not simply a reflection of increased fearfulness and "freezing". Rather, it is associated with stress-induced activation of opioid and, or non-opioid neurochemical mechanism [48,56] that reflects a motivational shift that facilitates the expression of various active and passive defensive behavioral responses [57], thereby reducing the risk of predation. The nature of the neurochemical mediation of the analgesic responses is dependent on the specific parameters of the threat, including the duration of exposure to predator odor [48,56].

Along with these behavioral effects, exposure to predators or their odors elicits alterations in the levels of hormones that are involved in stress responses. The presence of either a cat or the odors of a cat or other potential predators has been shown to acutely activate the adrenal–hypothalamic–pituitary (HPA) axis and markedly increase corticosterone levels in a variety of species of rodents (e.g. [7,52,58]). In parallel, acute predator or predator odor exposure also rapidly suppresses male testosterone levels [7,52].

4. Female odors and predator risk

The responses of male rodents to predator risk are sensitive to the actual or potential presence of a sexually receptive female. Male mice that were briefly pre-exposed to the odors of a sexually receptive female showed reduced avoidance and aversive responses and greater risk taking in the presence of predator odor. Brief (30 s–1 min), but not prolonged (15–30 min), pre-exposure to the odors (urine and, or bedding) of a novel, though not a familiar, sexually receptive female immediately decreased the aversion and avoidance responses of male mice to cat odor (cat collar) in an odor preference test (Fig. 1; and as previously shown [7,8]). Similarly, brief but not prolonged, pre-exposure to the odors of a sexually receptive female reduced the analgesic responses elicited by predator odor (Fig. 2; and as previously shown [7,8]). Brief pre-exposure to the female odors also attenuated the marked increases in corticosterone and decreases in testosterone levels that were induced in male mice by exposure to predator odor [7]. The presence of the odors of either a non-sexually receptive or ovariectomized female had no significant effects on male risk taking. The brief presence of the odors of a sexually receptive novel female, and likely transiently available female, leads to an enhanced sexual motivation, initiation of appetitive sexual responses and search by the male for the female.

Immediate prior sexual behavior has also been shown to influence responses to predator odor. Male rats engaging in sexual interactions prior to predator odor exposure exhibited reduced risk assessment behavior and increased hippocampal proliferation [59]. Similarly, acute predator (fox) odor exposure led to reduced exploratory behavior in reproductively inactive but not reproductively active male meadow voles [60]. These responses may again be associated with the enhanced interest in, and responses to, a potentially accessible sexually receptive female.

Although most prominent in rodents and several other nonhuman mammals, there is accumulating evidence that odor and associated cues are also used by humans in the context of sexual attraction and assessing an individual's reproductive potential (i.e. ovulation) and health (e.g. [61–66]). Consistent with the findings from mice, evidence from humans indicates that images of attractive, but not unattractive women, elicit risk taking, and that the extent of risk taking (as measured by a black-jack gambling task) may be affected by subtle ovulation cues associated with the phase of the menstrual cycle [6,17,67]. Men's testosterone levels are also suggested to be sensitive to women's ovulatory, but not non-ovulatory, odor cues in a manner reminiscent of that seen in male mice exposed to the odors of sexually receptive female [66]. Interpretation and extrapolation of the results of the studies with humans should, however, be tempered. For example, in the study of Miller and Maner [67] there was no significant change in pre- and post-smell testosterone levels

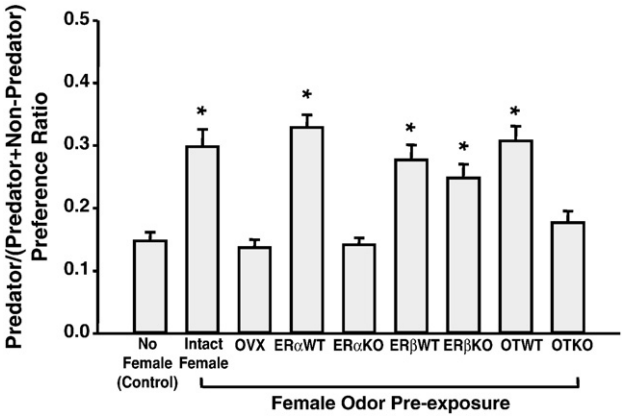

Fig. 1. Effects of a 1 min pre-exposure to the urine and bedding odors of a novel sexually receptive female on the subsequent responses of sexually naïve male mice in a Y-maze odor preference apparatus to a predator (cat odor) and non-predator (novel odor, almond), odor combination. Male mice were pre-exposed to the odors of either: an intact adult sexually receptive CD-1 female (intact female), an ovariectomized female (OVX) or an ERαWT, ERαKO, ERβWT, ERβKO, OTKO, or OTWT female. The responses of mice receiving no prior odor exposures (no female, control) are also shown. Responses are given as preference ratios (e.g. time spent in the vicinity of the predator odor/time spent in the vicinity of the predator odor + time spent in the vicinity of the non-predator odor). Preferences were determined over a 5 min time period. Increased preference indicates an augmented interest in, and approach to, the predator odor and is indicative of a reduced avoidance of the predator odor. Stars (*) indicate significant ($p<0.05$) increases in risk taking and reduced avoidance of predator odor. N = 10, in all cases. Vertical lines denote a standard error of the mean.

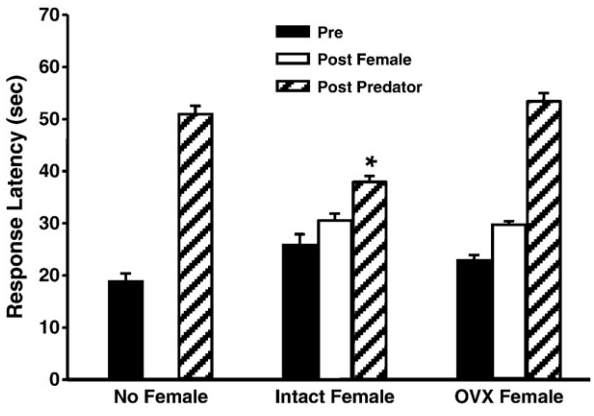

Fig. 2. Nociceptive responses of adult sexually naïve male mice that were pre-exposed for 1 min to the urine odors of either a sexually receptive intact CD-1-female (intact female) or an ovariectomized female (OVX) and then exposed for 1 min to predator (cat) odor. Responses of mice receiving no female odor exposure (no female) are also given. Nociceptive sensitivity, as measured by the latency of response to a 50 °C thermal surface, was determined before any odor exposures (baseline), after exposure to a female (post-female) and after exposure to the predator odor (post-predator). Stars (*) indicate a significant ($p<0.05$) decrease in predator odor induced analgesia. N = 10 in all cases. Vertical lines denote a standard error of the mean.

in the ovulation condition, rather merely a relative decline in the post-smell testosterone levels of the non-ovulation control group.

The effects of pre-exposure to female odor cues are also dependent on a male's sexual experience and history. In sexually experienced male mice exposure to the odors of a familiar sexually receptive female elicited reduced modifications in the behavioral and hormonal responses to predator odor. Likewise, exposure to the odors of either a non receptive or ovariectomized female had little effect in sexually experienced males, while some slight responses were evident in inexperienced, sexually naïve males [7]. The dependence on the presence of a novel female is suggestive of the "Coolidge Effect" reported for the effects of a novel female on male sexual behavior and testosterone [68]. This shows that it is the presence of a novel, and likely temporally limited, sexually receptive female, that elicits an apparent greater boldness in males. There is also evidence suggesting that the risk enhancing effects of women's cues on men may be modulated by prior familiarity and possibly male sexual experience, with extrapair sexual interest apparently augmenting acutely measured testosterone levels in human males [69].

5. Estrogen receptors and female odors

5.1. Introduction

The effects of female odors on male risk taking are natural menstrual and estrous cycle-related [7,8,70] raising an involvement of female sex hormones in determining odor characteristics and production. Pre-exposure to the odors of females in behavioral estrous led to enhanced risk taking by males as seen by a reduced avoidance of, and analgesic response to, predator odor, with the odors of either non-receptive or ovariectomized females having minimal effect [7,8]. In females of various vertebrate species their attractivity value depends upon the estrous cycle and especially estrogen levels (e.g. [23,35,36,71,72]). As estrogens are low in ovariectomized mice and higher in intact proestrus and diestrus females that are attractive to males [73], estrogens may be involved in determining the risk enhancing features of the female odors. In women features such as facial appearance, attractiveness of axillary sweat, olfactory cues of ovulation (fatty acid content in vaginal secretions) that can influence male behavior, change across the menstrual cycle [61–63,66,70,74,75]. Again while these effects are statistically significant they are limited in extent. For example, in one study [70] men demonstrated a slight but statistically above chance (61%), ability to discriminate between samples of the body odor of the same women collected on high- and low-fertility days. Men also showed a statistically higher (56%) than chance preference for women's high fertility odors. These qualitative shifts do parallel quantitative changes in estrogens and progesterone [65,76], supporting a putative involvement of estrogens and estrogen receptors in mediating the expression of women's ovulatory cues.

Estrogens primarily act through two nuclear hormone receptors, estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) which function as transcription factors and modulate gene expression, as well as more quickly through extranuclear cytosolic and membrane-bonded classic ERs, or membrane specific ERs that trigger a signal transduction cascade (see reviews in [10,11]). ERα and ERβ show both overlapping and nonoverlapping brain distributions, are expressed differently during development, and are encoded by different genes, which likely leads to the different roles they play in the regulation of physiology and behavior [10,11]. Studies using mice in which the gene for either ERα or ERβ was inactivated (knockout (KO) mice) showed that not only were there differences in social and sexual behaviors of the αERKO and βERKO mice [77–82], but also that there were differences in the sexual cues and, or signals they present. This was born out in studies showing that ERαKO and ERβKO male mice provided discriminably different odor cues and social and sexual incentive properties to female mice [71,83]. As described here this effect of ERs on the nature of the odor cues and their behavioral effects is also evident for female ERαKO and ERβKO mice.

5.2. Experiment 1. Effects of pre-exposure to female odor (ERαWT, ERαKO, ERβWT, ERβKO) on the responses of male mice to predator odor

5.2.1. Animals

Male mice (CD-1, 2–3 months of age) were individually housed in clear Plexiglas cages under a 12 h: 12 h light–dark cycle (lights 0800–2000 h) at 22 ± 1 °C with wood shavings bedding and food and water available ad libitum. All procedures were conducted in accordance with the Institutional Animal Care and Use Committee and the guidelines of the Canadian Council of Animal Care.

5.2.2. Apparatus

Odor responses of individual male mice were tested in a translucent Plexiglas Y-maze apparatus (5 cm in diameter) with 30 cm arms. The stimulus compartments at the end of the Y-maze in which the odor cues were placed, and the start box in which a male mouse was placed, were each 14 cm long. A solid Plexiglas barrier restricted the mouse to the start box, while perforated Plexiglas barriers at the ends of the two stimulus arms prevented contact with the odor sources while allowing detection of the odor. Removable solid Plexiglas barriers present at 'seams' 8 cm into each of the stimulus arms, prevented exposure of the mice to the odor cues until the designated test times.

5.2.3. Procedures

To minimize novelty responses, individual male mice (n = 10, per group) were placed in the apparatus and allowed to explore the various arms (after being held in the start box for 5 min) for 30 min on 2 consecutive days prior to testing. On the test day, a male mouse was placed in the start box of the apparatus for 15 min after which the solid barrier was removed allowing the mouse access to the two arms of the Y-maze. Two minutes later the Plexiglas barriers in the arms were removed exposing the mouse to the stimulus odors in each arm. During the subsequent 5 min, the duration of the time spent by a mouse in each arm within 8 cm of an odor source was recorded. The stimulus odor choice conditions were of a predator (cat) odor vs. non predator (control novel odor). Cat odor was provided by a 2 cm^2 strip of cloth collar worn by a cat for 2 weeks, while novel odor was provided by a 2 cm^2 strip of clean collar treated with dilute (10%) natural almond extract. Results of prior studies showed that the almond odor had no evident aversive effects on male mice [7,8].

'Preference' as used hereafter is defined as the duration of time spent in the stimulus arm of interest (cat odor) divided by the total time spent in the two stimulus arms. Preference here implies actively going to and inspecting/approaching the potentially threatening stimulus (cat odor). Increased preference indicates an augmented interest in, and approach to, the predator odor and is indicative of an enhanced risk taking and reduced avoidance of the predator odor. In this specific case "preference" actually implies "avoidance" as mice tend to avoid predator odors [7,8]. Hence, "increased preference" can be interpreted as a reduced "avoidance response" [84,85]. Preferences were determined over a 5 min period.

Testing of male mice in the Y-maze was carried out after a 1 min exposure to the odors of either; an intact adult sexually receptive (vaginal proestrus) CD-1 female (intact female), an ovariectomized female (OVX, at least 2 weeks before odor collection), or an ERαWT, ERαKO, ERβWT, ERβKO female. Both ERα and ERβ have been shown to be involved in the regulation of oxytocin (OT) production [10–12], with females being able to distinguish between the odors of oxytocin wildtype (OTWT) and OT knockout (OTKO) males [71]. As such, the roles of oxytocin were also considered and determinations

were made of the effects of pre-exposure to the odors of OTWT and OTKO females on the responses of male mice to predator odor. The responses of male mice receiving no prior odor exposures (no female, control) were also recorded.

Adult female ERαKO, ERβKO, ERαWT, ERβWT, OTWT and OTKO mice (25–30 g; 7–12 months of age) used for the odor sources were obtained from breeding colonies maintained at The Rockefeller University (New York, NY) by mating heterozygous male and female mice. The genotype of each mouse was determined by PCR amplification of tail DNA. Prior to odor collection all of the mice were individually housed for 2–3 weeks in Plexiglas cages under a 12 h:12 h light dark cycle (lights off at 1000 h) at 22 ± 1 °C with food and water available ad libitum (additional details of the mice are provided in [77]).

During the odor exposures male mice were individually placed in a Plexiglas partitioned area (12.5 × 15 × 10 cm) that was provided with a vented Plexiglas tube, 10 cm in length, 3 cm in diameter and sealed at each end with fine plastic mesh across which a mouse could neither traverse nor reach. The ends of the tube contained the urine and associated bedding odors of a female to which the male could come into close olfactory contact. Freshly deposited urine and associated odors were obtained from single females that were placed for 1 h in a clean cage lined with blank filter paper (Whatman No. 4, England). Each male was presented with the odor of a single female. Wet mount vaginal smears were used to determine the estrous state of the females.

5.2.4. Data analyses

All preference ratios were transformed to natural log (ln) values prior to analysis by analysis of variance (ANOVA) followed by post-hoc Tukey's tests. A 0.05 significance level was used throughout.

5.2.5. Results

Male mice displayed a marked overall avoidance of predator odor, with only 16–20% of their time being spent in the vicinity of the cat odor. Pre-exposure to female odor significantly reduced predator avoidance [$F(8,81) = 15.15$; $p = 0.000$]. Pre-exposure to the odors of ERαWT, ERβWT, ERβKO, and OTWT females significantly reduced the avoidance of the predator odor (all ps < 0.05), though in all cases the mice still showed a significant, but attenuated, avoidance of the predator odor, now spending 27–33% of their time in the vicinity of the predator. In contrast, pre-exposure to the odors of either an ovariectomized (OVX), ERαKO, or OTKO female had no significant effect on the avoidance of the predator odor.

5.3. Experiment 2. Effects of pre-exposure to female odors on predator-induced analgesia in male mice

5.3.1. Procedures

Nociceptive responses of sexually naïve adult male mice (as described in Experiment 1) that were exposed for either 1 min to the urine odors of either a sexually receptive intact CD-1-female (intact female) or an ovariectomized female (OVX) and then exposed for 1 min to predator (cat) odor (odor exposures as described in Experiment 1) were determined. Responses of mice receiving no female odor exposure (no female) were also made. Nociceptive sensitivity, as measured by the latency of response to a 50 °C thermal surface (analgesiometer, AccuScan Instruments, Columbus OH), was determined before any odor exposures (baseline), after exposure to a female odor (post-female), and after exposure to the predator odor (post-predator). Animals were placed on the warm surface and the latency of the first foot lift or lick, whichever came first, was recorded. After these responses were displayed, or after 60 s, the mouse was quickly removed from the surface and returned to his cage.

5.3.2. Results

Data were analyzed with a repeated measures ANOVA followed by Tukey's post-hoc tests. The overall analysis incorporates responses to both urine and bedding odors (not shown) and ER and OT treatments that are described in Experiment 3 and shown in Fig. 4. There was an overall significant effect of odor exposure ($F(6,108) = 35.63$, $p = 0.00$); a significant effect of time (pre-post) ($F(2, 216) = 799.6$, $p = 0.000$); no effect of (difference between) urine and bedding ($F(1,60)$ 0.30, $p > 0.50$) and no significant interaction between urine/bedding and odor exposure ($F(4,108) = .917$, $p = .457$). There was, however, a significant interaction between urine/bedding, odor and time (pre-post) ($F(8,210) = 2.978$, $p = .009$).

Males that were exposed to the cat odor showed significantly ($p < 0.01$) increased thermal responses indicative of the induction of the analgesia. Pre-exposure to the odor of the intact female significantly ($p < 0.05$) reduced the level of analgesia, while pre-exposure to the odors of the OVX female had no significant effect on analgesic responses. Exposure to the female odor per se had no significant effect on the response latencies.

5.4. Experiment 4. Female odors, ERα, ERβ and initial odor choices of males

The roles of ERs in the production of odor cues was further considered with the ERα agonist, 4,4′,4″-(4-Propyl-[1H]-pyrazole-1,3.5) (PPT), which has 410 times more selective activity on ERα over ERβ [86], and the ERβ agonist, 7-Bromo-2-(4-hydroxyphenyl)-1,3-benzooxazol-5-ol (WAY-200070), which is 68 more times selective for ERβ than ERα [87]. Administration of these agonists (ERβ (WAY-200070) 30 and 90 mg/kg i.p.; αER (PPT) 0.10 mg/kg i.p., 72 h prior) had significant effects on the social behavior of ovariectomized female mice, thus confirming the effectiveness of these administrations in the females [88,89].

The ability of males to distinguish the odors of OVX females treated with the ERα and ERβ agonists was examined prior to determining the effects of these odors on male predator responses. This was done with an initial choice test, which assesses which odors an individual finds more attractive, or salient in a socio-sexual context [84,85]. This was conducted with both sexually naïve and sexually experienced males as prior sexual experience has been indicated to influence a male's responses to female odors [7].

5.4.1. Animals

Male mice (CD-1, 2–3 months of age) were individually housed in clear Plexiglas cages under a 12 h:12 h light–dark cycle (lights 0800–2000 h) at 22 + 1 °C with wood shavings bedding and food and water available ad libitum. The males consisted of two groups. One group (sexually naïve) was composed of virgin males that had no prior exposure to the odors of unrelated females. The other group (sexually experienced) was housed with an adult female for 1 week before being housed singly for the experiment.

5.4.2. Procedures

Initial odor choices of the individual sexually experienced and sexually naïve male mice were recorded in a clean cage (25 cm × 15 cm × 20 cm) in which a vented Plexiglas tube (10 cm in length, 3 cm in diameter and sealed at each end with plastic mesh) was placed. Each end of the tube contained a different odor source. The first odor to which a male ($n = 15$, in each group) went to and remained for a minimum of 10 s was considered to be the initial odor choice. The odor choice combinations consisted of: either an intact female in behavioral estrous (intact female; CD-1, 20–25 g), an ovariectomized female (OVX) or an ovariectomized female treated with either an ERβ agonist (WAY-200070, 30 mg/kg, 72 h prior) (OVX + ERβ), an ERα agonist (PPT, 0.10 mg/kg, 72 h prior) (OVX + ERα) or the vehicle (OVX (Veh) sesame

oil, 10 ml/kg, 72 h prior) (details of the female mice are provided in [89,90]). The specific odor combinations examined are listed in Table 1.

5.4.3. Data analyses

Initial choice data were analyzed by chi-square tests. A 0.05 significance level was used throughout.

5.4.4. Results

The initial odor choices displayed by the males in the various stimulus odor combinations are shown in Table 1. In the OVX–behavioral estrous and OVX (Veh)–behavioral estrous stimulus odor combination both the sexually experienced and naïve males showed a highly significant ($p<0.001$) initial choice for the odors of the intact behaviorally estrous females. In the OVX (Veh)–OVX (ERα) stimulus odor combination the sexually experienced males showed a significant ($p<0.01$), and sexually naïve a non-significant ($p=0.07$), choice of the odors of OVX females that had received prior treatment with the ERα agonist. In the OVX (Veh)–OVX (ERβ) odor combination both the sexually experienced and naïve males showed a significant initial choice of the odors of the OVX females previously administered the ERβ agonist. In the behavioral estrous–OVX (ERα) and behavioral estrous–OVX (ERβ) stimulus combinations both the experienced and naïve males showed no significant differences in their initial choices going equally to both odors. There were no significant differences in the initial choices of the OVX–OVX (Veh) stimulus odor combinations.

5.5. Experiment 5. Effects of pre-exposure to female odor (OVX + ERα, ERβ, agonists) on the avoidance responses of males to predator odor

5.5.1. Procedures

The effects of a 1 min pre-exposure to the urine odors of: either an intact behaviorally estrous female (intact female; CD-1, 20–25 g), an ovariectomized female (OVX) or an ovariectomized female treated with either an ERβ agonist (WAY-200070, 30 mg/kg, 72 h prior) (OVX + ERβ), ERα agonist (PPT, 0.10 mg/kg, 72 h prior) (OVX + ERα) or the vehicle (sesame oil, 10 ml/kg, 72 h prior) (details of the female mice are provided in [89,90]) on the predator avoidance responses of sexually naïve male mice ($n=10$) (males as described in Experiment 1) were examined. The responses of males receiving no prior odor exposures (no female) were also determined. Responses are given as preference ratios (e.g. time spent in the vicinity of the predator odor/time spent in the vicinity of the predator odor + time spent in the vicinity of the non-predator odor (novel almond odor)) (details of the procedures are given in Experiment 1). Preferences were determined over a 5 min period.

5.5.2. Data analyses

All preference ratios were transformed to natural log (ln) values prior to analysis by analysis of variance (ANOVA) followed by post-hoc Tukey's tests. A 0.05 significance level was used throughout.

5.5.3. Results

Male mice displayed a marked overall avoidance of predator odor, with only 16–20% of their time being spent in the vicinity of the cat odor. This avoidance was affected by pre-exposure to female odor with a significant effect of female pre-exposure [$F(5,54)=25.35$; $p=0.0001$]. Brief pre-exposure to the odors of a female in behavioral estrous, OVX + ERα, OVX + ERβ, significantly reduced the avoidance of the predator odor (intact female $p<0.001$; other ps <0.05), though in all cases the mice still showed a significant ($p<0.05$), but attenuated, avoidance of the predator odor. As well, pre-exposure to the odors of either the OVX + ERα or OVX + ERβ females resulted in a significantly ($p<0.05$) less attenuation of the predator odor avoidance than did the odors of the intact female in behavioral estrous. Pre-exposure to the odors of either an OVX or OVX + vehicle female had no significant effect on the avoidance of the predator odor.

5.6. Experiment 4. Effect of pre-exposure to female odor (OVX + ERα, ERβ, agonists) on predator-induced analgesia in male mice

5.6.1. Procedures

Determinations were made of the nociceptive responses of adult sexually naïve male mice ($n=10$) that were exposed for 1 min either to the urine odors of either a CD-1 female in behavioral estrous (intact female), an ovariectomized female (OVX), or an ovariectomized female treated with either an ERβ agonist (WAY-200070, 30 mg/kg and 90 mg/kg, 72 h prior) (OVX + ERβ), or the vehicle (sesame oil, 10 ml/kg, 72 h prior) (details of the female mice are provided in [89,90]) and then exposed for 1 min to cat odor (odor exposures as described in Experiment 2). Nociceptive sensitivity, as measured by the latency of response to a 50 °C thermal surface, was determined before any odor exposures (baseline), after exposure to a female odor (post-female) and after exposure to the predator odor (post-predator).

5.6.2. Data analyses

Data were analyzed with a repeated measures ANOVA followed by Tukey's post-hoc tests with the results described in Experiment 2.

5.6.3. Results

Males that were exposed to the cat odor showed increased thermal response latencies ($p<0.01$) indicative of the induction of the analgesia (Fig. 2). Pre-exposure to the odors of the OVX + ERβ (30 or 90 mg) significantly reduced the level of analgesia ($p<0.01$) while pre-exposure to the odors of the OVX female had no significant effect on analgesic responses (Fig. 4). Exposure to the female odor per se had no significant effect on the response latencies.

5.7. Discussion

As shown in Figs. 1 and 2 pre-exposure to the odors of the ERαKO female mice, in comparison to their wild type (ERαWT), had no significant effect on the responses of males to predator odor and their risk taking, whereas pre-exposure to the odors of ERβKO females increased risk taking in a manner similar to that seen in their wild types (ERβWT). It should be noted that αERKO female mice do not ovulate, have high serum androgen levels, and enlarged clitoral glands [91,92], which could lead to the production of disrupted odor cues.

Table 1
Initial odor choices of sexually experienced and sexually naïve male mice when presented with the odors of a female that is either in behavioral estrous, ovariectomized (OVX), OVX treated with either the ERα agonist, PPT (0.10 mg/kg), and ERβ agonist, WAY00090 (90 mg/kg), or their sesame oil vehicle (Veh). P values indicate the result of the χ^2 comparison to 50% random choice. Bolded font indicates statistically significant ($p<0.05$) comparisons.

Choice presented		Percent initially choosing specific odor (p-value)	
	Initial choice	Naïve	Experienced
OVX–behavioral estrous	Behavioral estrous	**86 ($p=0.0045$)**	**93 ($p=0.0008$)**
OVX (Veh)–behavioral estrous	Behavioral estrous	**86 ($p=0.0045$)**	**93 ($p=0.0008$)**
OVX (Veh)–(ERα agonist)	(ERα agonist)	73 ($p=0.07$)	**86 ($p=0.0045$)**
OVX (Veh)–OVX (ERβ agonist)	OVX (ERβ agonist)	**80 ($p=0.02$)**	**86 ($p=0.0045$)**
Behavioral estrous–OVX (ERα agonist)	(ERα agonist)	47 ($p=0.49$)	40 ($p=0.47$)
Behavioral estrous–OVX (ERβ agonist)	OVX (ERβ agonist)	53 ($p=0.79$)	47 ($p=0.79$)
OVX (Veh)–OVX	OVX	53 ($p=0.79$)	60 ($p=0.47$)

In this context, the effects of deletion of the genes for oxytocin (OT; OTKO and OTWT female) were also examined. Oxytocin is a neuropeptide hormone that plays a prominent role in socio-sexual behavior and importantly is under the regulation of ERα and ERβ (see below and [10,11]). Moreover, OT has been shown to not only initiate and maintain female sexual behavior [93], but also the odors of animals with elevated OT levels have been shown to have anxiolytic effects [94,95], raising the possibility of an influence on male responses to predator threat. In addition, as seen with the ERs, there were differences in the sexual cues and signals that the OTWT and OTKO male mice presented to females [71,83]. As for the ERs this effect of OT on odor cues was also found for males with pre-exposure to the odors of the OTKO females, resulting in significantly less risk taken by males than pre-exposure to the odors of OTWTs (Fig. 1). Interestingly, human participants after only a 20 s silent observation period could also distinguish between both males and females that differed in their expression of alleles for the oxytocin receptor and likely OT levels [96]. Whether or not these differences in OT and associated cues and signals involves changes in ER related mechanisms remains to be determined. As well, the effects of progesterone on female odor cues and their behavioral effects need to be considered.

The results of the initial choice tests confirmed that both sexually experienced and naïve males could distinguish between the odors of ovariectomized females and females in behavioral estrous, displaying an immediate heightened interest in the odors of sexually receptive females. These results further showed that both naïve and experienced males could distinguish between the odors of OVX females and OVX females that had received prior treatment with the ERα and ERβ agonists, and that they responded to these odors in a similar manner as to the odors of females in behavioral estrous. It should be noted that initial choices and preferences are not necessarily equivalent and do reflect different aspects of social and sexual interest and responses [85].

Brief pre-exposure to the urine and, or bedding odors of females that had received the ER agonists also affected the risk taking responses of males, reducing both the avoidance of, and analgesic responses to, predator odor (Figs. 3, 4). These findings showing that the attenuation of the risk enhancing effects of the odors of ovariectomized females could be reversed by treatment with ERα and ERβ agonists further supports a role for estrogens in determining risk reducing properties of the female odors. Whether the effects of the ERβ agonist arise through actions on ERα, OT and, or through other neurohormonal and neurotransmitter receptor mechanisms remains to be determined.

The odor responses of the male mice may be elicited by either relatively short-lived highly volatile and, or non-volatile (involatile) female odor cues that are detected upon close inspection of the urinary and bedding cue [97–99]. Volatile and non-volatile odors associated with the major histocompatibility complex (MHC) and the major urinary proteins (MUPs), respectively, provide information about the condition and individual identity of the scent owner [97,98,100]. The MHC is a large cluster of polymorphic genes coding for molecules involved in the immune response. ERα and ERβ have modulatory effects on immune function and likely the associated olfactory cues (e.g. [101,102]). In addition, ERs could influence other central and peripheral systems associated with the expression of odor constituents (e.g. vaginal odor constituents in humans [103]). Together, these ER modulated odor signals can provide information about the condition and identity of the female that can influence the behavior of males.

6. Estrogen receptors and male risk taking

The enhanced risk taking evident in males after exposure to female cues incorporates two aspects. One is a sexual component involving a response to a sexually receptive female and/or her cues, while the other consists of a social recognition element involving the distinction between a novel and familiar individual. These two components allow males to selectively respond to sexually receptive and potentially accessible novel females, likely increasing a male's reproductive fitness. This sexual incentive could elicit a rapid motivational shift in the males from defensive and avoidance responses to a predator threat to a search for, and approach to, a novel sexually receptive female that may be present for only a limited time period. Human decisions that are made in the context of risk, including those associated with sexual responses, have also been found to be malleable and, thus, likely also dependent on the nature of the opportunities available [13,104,105].

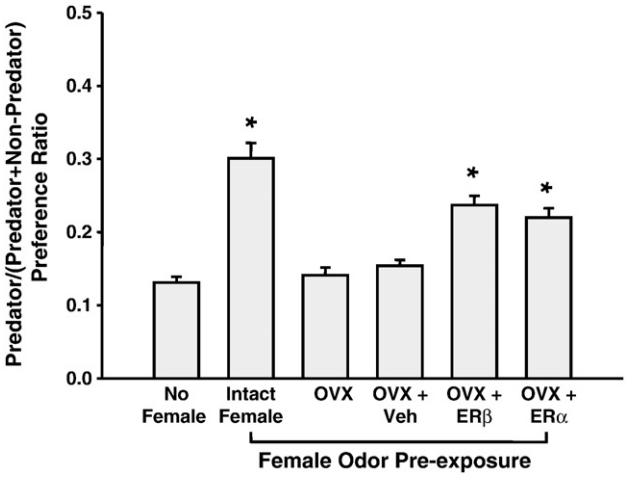

Fig. 3. Effects of a 1 min pre-exposure to the urine and bedding odors of a novel female on the subsequent responses of male mice in a Y-maze odor preference apparatus to a predator (cat odor) and non-predator (novel odor, almond), odor combination. Male mice were pre-exposed to the odors of either: a sexually receptive intact CD-1 female (intact female), an ovariectomized female (OVX), or an ovariectomized female treated with either an ERβ agonist (WAY-200070, 30 mg/kg, 72 h prior) (OVX + ERβ), ERα agonist (PPT, 0.10 mg/kg, 72 h prior) (OVX + ERα) or the vehicle (Veh, sesame oil, 10 ml/kg, 72 h prior). The responses of mice receiving no prior odor exposures (no female, control) are also shown. Responses are given as preference ratios (e.g. time spent in the vicinity of the predator odor/time spent in the vicinity of the predator odor + time spent in the vicinity of the non-predator odor). Preferences were determined over a 5 min time period. Increased preference indicates an augmented interest in, and approach to, the predator odor and is indicative of a reduced avoidance of the predator odor. Stars (*) indicate significant ($p<0.05$) increases in risk taking and reduced avoidance of predator odor. $N=10$, in all cases. Vertical lines denote a standard error of the mean.

The neurobiological mechanisms that underlie social and sexual behaviors and responses (e.g. [9–12,106–108]) as well as those that affect risk-taking and boldness (e.g. [13,105,109–111]) are coming under increased scrutiny. There is substantial evidence that estrogens and ERs have an important role in determining various aspects of social and sexual behavior both in males and females, as well as in influencing decision making [10,11]. ERαKO and ERβKO male mice were impaired in their olfactory-mediated social recognition [77,92,106,107]. ERαWT male mice displayed normal sexual behavior and mating with estrous females, while ERαKO males failed to do so, though they apparently show normal responses to, and interests in, the odors of estrous females ([79–82]; see, however, [113,114]). In contrast, the lack of a functional ERβ, while affecting social recognition [77,115], did not impair normal expression of adult male sexual behavior or preferences for females. Both ERβWT and ERβKO male mice expressed an interest in, and responses to, female olfactory cues and exhibited normal sexual behavior, as well as enhanced intermale aggression [79–82,116]. Thus, ERα seems to be involved in the mediation of both social responses and sexual behaviors, while ERβ seems to be involved with social responses but not sexual behaviors. However, the alterations seen in the behaviors of ERαβKOs also

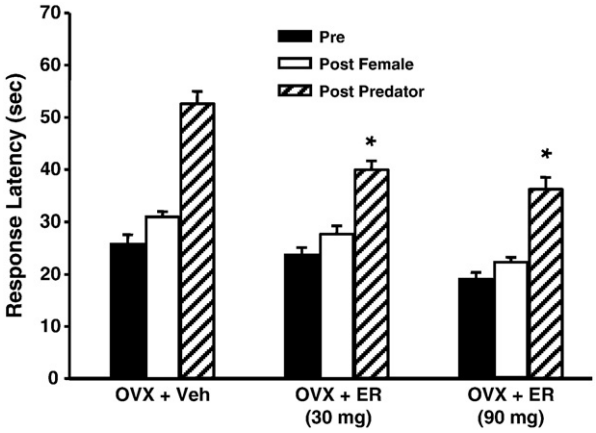

Fig. 4. Nociceptive responses of adult sexually naïve male mice that were pre-exposed for either 1 min to the urine odors of either a sexually receptive intact CD-1 female (intact female), an ovariectomized female (OVX), or an ovariectomized female treated with either an ERβ agonist (WAY-200070, 30, 90 mg/kg, 72 h prior) (OVX + ERβ) or the vehicle (sesame oil, 10 ml/kg, 72 h prior) and then exposed for 1 min to predator (cat) odor. Nociceptive sensitivity, as measured by the latency of response to a 50 °C thermal surface, was determined before any odor exposures (baseline), after exposure to a female odor (post-female) and after exposure to the predator odor (post-predator). Stars (*) indicate a significant ($p<0.05$) decrease in predator odor induced analgesia N = 10, in all cases. Vertical lines denote a standard error of the mean. N = 10, in all cases.

suggest some interplay and, or interactions between ERα and ERβ [10,11]. As well, the possible roles of other membrane ER receptors need to be considered.

ERαWT and ERβWT males that were briefly exposed to the odors of a novel, but not a familiar female, exhibited enhanced risk taking with the males displaying reduced avoidance of, and analgesic responses to, predator (cat) odor [8]. On the other hand, the ERαKO males failed to show any reduction in their aversive responses to predator odor after exposure to female odors, while the ERβKO males, although they displayed greater risk taking, failed to distinguish between novel and familiar females and their responses were no longer linked to novel sexually receptive females. In both cases the males did, however, show normal olfactory responses. These findings suggest that ERα may be associated with the sexual mechanism (response to novel sexually receptive female) and ERα and ERβ with the social (recognition of and motivation to approach a female) mechanisms associated with the effects of female cues on risk taking in males. These findings also raise the possibility that genes for ERα and ERβ may also have a modulating role on sexually motivated risk taking and decision making in men.

These differential effects on risk taking are consistent with other studies with ERKO mice showing a differential involvement of the two ERs in sexual and social behavior. ERα and ERβ often have antagonistic actions and transcription effects leading to potentially different behavioral effects [117,118]. It is consistent with the extent of attenuation of social memory in αERKO and βERKO mice [77,115]. Loss of ERα is reported to result in a decrease of both male and female sexual behaviors with no evident effects of ERβ deletion [78–82,114,116,119]. Although, in both cases the KOs could still distinguish between males and females of various sexual conditions, there are some suggestions that αERKOs may show a decrease in sexual incentive motivation [114]. In addition, ERαKO males displayed reduced aggressive behavior towards other males, while ERβKO males displayed enhanced intermale aggressiveness relative to their WTs [78–82,92,113,116,120]. It has been suggested that ERβ activation may exert an attenuating effect on male aggression induced by estrogen through ERα mediated mechanisms [121].

These findings are consistent with a proposed "micronet" involving genes for ERα, ERβ, oxytocin (OT), and the OT receptor (OTR) as the regulatory basis for olfactory mediated social recognition [106,107]. As noted earlier, it may also relate to the reduced effects that the odors of OTKO females have on male risk taking. Oxytocin has been shown to augment "trust" and the use of information provided by others in mice and humans (e.g. [112,122,123]). Both of these actions could influence responses to aversive stimuli and sexually motivated decision making and influence risk taking [122]. In addition, there is evidence that ERs have effects on various aspects of socially, and likely sexually, associated cognitive functions [10,11,88–90,124].

Olfactory signals from the main and accessory olfactory pathways converge at the medial amygdala where the identity of the odor source is most likely determined. Under the influence of ERβ, OT synthesis is increased by estradiol in the hypothalamus [125], whereas estradiol bound to ERα increases transcription of the OTR in the amygdala [126]. Disruptions at the level of either OT, ERα or ERβ genes and their products could lead to impaired processing and, or integration, of odor information at the level of the medial amygdala. This could result in impaired discrimination between familiar and unfamiliar female odor, thus, modifying social and sexual motivation. This is supported by the findings that exposure to the signals of a sexually receptive female results in the activation of brain OT at the level of the paraventricular nucleus of the hypothalamus [95] that may be associated with an anxiolytic response and reduced emotional response to anxiogenic stimuli in a manner that is consistent with an enhanced risk taking and boldness.

These risk enhancing effects of female odor may also involve alterations in the metabolism of testosterone. Aromatase activity can change quickly in the brain in response to external stimuli [127]. Local testosterone aromatization can rapidly control estrogen concentrations in a time frame compatible with the rapid changes in male risk taking seen after exposure to female odors. Increased aromatase activity with subsequent alterations in testosterone metabolism, shifts in central estrogen levels, and possibly ER function, have been proposed to be associated with augmented male sexual interest [128–130]. This is in agreement with the findings that non-copulating rats, while having similar testosterone levels as copulating rats, display reduced neuronal aromatase (Ar) activity and levels of ERα [131,132]. ArKO mice have a similar social and sexual phenotype as the ERαKO [128,133] further supporting the idea of aromatase and ERα dependent responses.

Aromatase is also extensively distributed in the human brain, with the highest concentrations found in the amygdala [134]. Results of recent studies have shown that in both men and women constraint scores (which reflect risk taking) are correlated with aromatase activity in the amygdala [135]. This raises the possibility that ERα and ERβ may also influence risk taking and associated decision making in humans. However, whether or not central aromatase and ERs are involved in mediating the rapid effects of female cues in human males still remains to be explored.

Dopamine (DA) and the DA system which are associated with the activity of reward pathways and responses to sexual stimuli are also involved with risk taking [136]. Different modes of DA circuits, including the basolateral amygdala, anterior cingulate and nucleus accumbens, in rodents have shown to be associated with decision making, including that related to risk [137–139]. In humans the effects of female stimuli on financial risk taking have been proposed to be associated with a change in affect and neural activation and the activation of reward associated areas (e.g. nucleus accumbens) that modify risk preferences as well as learning [99]. Estradiol exerts a complex modulation of DA. Estrogens have been shown to enhance the activity of the DA system, by both increasing DA release [140,141] and decreasing DA reuptake by the dopamine transporter [142]. Also ERs affect DA by acting through ER and estrogen stimulating progesterone expression [11,12]. Estradiol and ERα and ERβ agonists also exert dose related effects on cognition mediated by regions thought to be involved in learning and decision making (e.g. [124,143]). As well, estrogens influence glutamate transmission within certain

nodes of the mesocorticolimbic circuitry that affects DA and decision making [143]. In concert with the important role played by hypothalamic DA in the control of male sexual behavior, and the manner in which steroid hormones interact with DA transmission to sensitize sexual responses (e.g. [136,144,145]), this raises additional mechanism whereby ERs could influence male risk taking and the impact of female cues.

7. Conclusions

Male risk taking is sensitive to either the presence of a female, or cues associated with, a sexually receptive female. In rodents, estrogens appear to have a particularly significant role in determining the risk enhancing properties of the odors of sexually receptive females. The enhanced risk taking elicited by brief exposure to female odors is also modulated by estrogen receptors, with ERα being associated with the sexual mechanisms (response to sexually receptive female) and ERβ with the social (recognition of and approach to a novel female) mechanisms that can facilitate mate search. The greater risk-taking or male boldness may also be related to the lower fear and stress responses and greater sexual motivation and "searching" for a briefly available sexually receptive novel female. Augmented sexual motivation is similarly indicated to contribute to the greater risk taking seen in men exposed to sex related cues of women [1–5,14–19]. This raises the possibility that ER related mechanisms may have a similar involvement in mediating the effects of female sexual cues and signals on male risk taking in humans.

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