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The role of conditioning on heterosexual and homosexual partner preferences in rats

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Partner preferences are expressed by many social species, including humans. They are commonly observed as selective contacts with an individual, more time spent together, and directed courtship behavior that leads to selective copulation. This review discusses the effect of conditioning on the development of heterosexual and homosexual partner preferences in rodents. Learned preferences may develop when a conditioned stimulus (CS) is associated in contingency with an unconditioned stimulus (UCS) that functions as a reinforcer. Consequently, an individual may display preference for a partner that bears a CS. Some UCS may be more or less reinforcing, depending on when they are experienced, and may be different for males and females. For example, it could be that, only during periods of early development, that stimuli associated with nurture and juvenile play become conditioned. In adulthood, other stimuli such as sexual reward, cohabitation, mild stress, or even pharmacological manipulations may function as reinforcers to condition partner preferences. Evolutionary biologists and psychologists must take into consideration the idea that an individual's experience with reward (i.e. sexual and pharmacological) can override presumably 'innate' mate choices (e.g. assortativeness and orientation) or mate strategies (e.g. monogamy or polygamy) by means of Pavlovian and operant contingencies. In fact, it is likely as innate to learn about the environment in ways that maximize reward and minimize aversive outcomes, making so-called 'proximate' causes (e.g. pleasure) ultimately more powerful predictors of social behavior and choice than so-called 'ultimate' causes (e.g. genetic or reproductive fitness).

Keywords: *pavlovian*; *operant*; *learning*; *sex*; *copulation*

Partner preferences occur in many social species, including humans. A preference is commonly observed as selective contacts with an individual, more time spent together, and directed courtship behavior that leads to selective copulation. In general, species with non-exclusive partner preferences are referred to as polygamous. Those species may express preference for a particular partner, but it lasts only for periods of mating. Furthermore, the preference may not be for a particular individual or features of an individual but rather for the overall display of sexual receptivity. On the other hand, species that display exclusive and long-lasting preferences toward one particular partner are usually referred to as monogamous. A monogamous individual will display a very selective preference to court, copulate, nest-build, and raise offspring, with a particular partner that bears specific and recognizable features (Coria-Avila, 2007). In addition, some researchers agree upon the idea that monogamous species that have developed a pair bond may aggressively reject unfamiliar conspecifics, including additional potential mates (Aragona et al., 2006; Carter, DeVries, & Getz, 1995; Wang, Hulihan, & Insel, 1997; Winslow, Hastings, Carter, Harbaugh, & Insel, 1993).

Partner preferences are the result of a systematic interrelationship between genetic mechanisms, hormonal effects, and learning. For example, an individual can be born with the genetic information that directs brain organization and the hormonal profile that facilitates the sensitivity to respond toward a particular type of partner, which generally occurs toward a sexually mature individual of the opposite sex. However, starting at birth, animals can learn new preferences based on exposure to individuals of their own species. This early contact facilitates phenomena such as imprinting (Batenson, 1978), in which the first conspecific-related stimuli sensed during critical periods of development can direct future partner preferences. Consequently, the partner preference observed in a sexually naïve adult individual may be the

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result of innate factors combined with early learning experiences during critical periods. In addition, all individuals can develop new preferences or aversions throughout the life span and make new associations in order to pursue pleasure and avoid pain. Accordingly, adult partner preferences may become conditioned to stimuli that have become predictors of sexual reward (or other types of reward). Thus, in the presence of a predictor of reward, partner preference may be facilitated or more easily expressed, whereas, in the presence of a negative predictor, a partner may be avoided, devaluated, or even aversive. As a consequence, 'innate' partner preferences (e.g. for assortative features) or mate strategies (e.g. monogamy or polygamy) may become further narrowed or even changed by subsequent conditioning in adulthood by features associated specifically with reward.

Partner preferences can be studied from different perspectives. For example, from a biological point of view, it is important to study the consequences of having a partner preference on the survival and reproductive fitness of a species. From the psychological perspective, partner preferences are studied because they can lead to social attachments, referred to as pair bonds in some animals and 'romantic love' in humans; and disruption of established attachments, or the incapacity to form new ones, can have negative effects on mental health (Insel & Young, 2001). Thus, understanding the bases of partner preference formation is necessary to understand an important part of social behavior in animals and humans.

The aim of this manuscript is to discuss the role of learning on the expression of heterosexual and homosexual partner preferences in rodents. Toward this goal, I will describe the mechanisms of Pavlovian and instrumental (operant) conditioning. In addition, I will provide evidence on how these two learning mechanisms are relevant during critical periods of development, including the early postnatal and juvenile periods. However, I will discuss how 'other critical periods' are open during the experience of sexual reward in adulthood or *via* pharmacological treatments.

Pavlovian conditioning of partner preference

Pavlovian or classical conditioning refers to an association that is formed between two stimuli (Pavlov, 1927). For example, under normal circumstances, unconditioned stimuli (UCSs) will elicit physiological unconditioned responses (UCRs). UCRs are those unlearned responses already present in an animal's natural repertoire. UCSs are natural stimuli that normally elicit UCRs in a presumably hardwired stimulus-response (S-R) neural connection. Neutral stimuli, however, will not trigger any UCR, but if properly paired in contiguity and contingency with an UCS, animals can make a predictive association between the neutral stimulus and the UCS, which then triggers the UCR. When a neutral stimulus is capable of triggering a response that was not present before learning, it is referred to as a conditioned stimulus (CS), and the response is referred to as a conditioned response (CR). When this occurs, it is believed that the CS elicits a representation of the UCS at a neural level.

There are different ways in which Pavlovian conditioning can affect sexual behavior and, ultimately, the expression of partner preference. First, a mate can be seen as a conjunction of multiple stimuli. Some of those stimuli may function as UCS, which trigger UCRs, but many others are ineffective because they fail to initially trigger any UCR (Kippin & Pfaus, 2001). Ineffective natural stimuli (i.e. coat color in a male rat) may become associated with UCSs (i.e. paced intromissions from him) through sexual experience and, in turn, may be able to elicit CRs (i.e. sexual motivation) (Coria-Avila et al., 2006). Also, originally neutral or ineffective stimuli (i.e. almond odor) can become conditioned if are paired in contingency with the UCS (Coria-Avila, Ouimet, Pacheco, Manzo, & Pfaus, 2005; Kippin, Cain, & Pfaus, 2003). It is possible that conditioning of partner-related stimuli occur during several periods of life. However, some well-characterized critical periods include the early postnatal weeks, adolescence, or periods associated with an specific pharmacological treatment.

Early postnatal period

Certain stimuli that are sensed during early critical periods of life become associated through Pavlovian conditioning with innate rewards (e.g. maternal care, nutrient intake, etc.). This type of conditioning is termed 'imprinting' and can strongly affect sexual preferences in adulthood (Batenson, 1978). This conditioning occurs at young age when the brain is especially sensitive to make new associations. Imprinting usually occurs to the features of parents and species and is considered the first step in the phenomenon of assortative mating, in which animals choose to mate selectively with members of their own strain relative to members of a different strain or species that are genetically less similar. Assortative mating is believed to maintain homozygosity in a strain and, thereby, keep strains from outbreeding positive characteristics. In humans, assortative mating might occur when people display partner preference for phenotypic (e.g. racial, facial, etc.), social (e.g. cultural/religious beliefs), and personality characteristics (e.g. introversion/extroversion) that are somewhat similar to one's own (Luo & Klohnen, 2005; Malina, Selby, Buschang, Aronson, & Little, 1983; Salces, Rebato, & Susanne, 2004), which would naturally result from the fact that people are more likely to interact harmoniously with others with similar attitudes/manerisms.

There is evidence indicating that males of different species can develop sexual imprinting for mates that bear cues associated with the female that nursed them or cues

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associated with the nursing period. In one study, for example, neonatal rats were nursed by their biological mother, which had a neutral odor (lemon) applied on her abdomen. At the appropriate time, the males were weaned and never exposed to the scent again, until about 100 days of age, when they were paired with scented or unscented unfamiliar females for copulation. The results indicated that males exposed in the early postnatal period to a lemon scent, displayed shorter ejaculation latency with lemon-scented females when they grew up, relative to the ejaculation latency observed when they were exposed to non-scented females (Fillion & Blass, 1986). That experiment was one of the first to demonstrate that neutral odors that are sensed during early periods can increase sexual excitement during future sexual encounters. In that case, a stronger sexual excitement was observed as shorter ejaculation latency with a receptive female bearing the odor.

Other experiments with imprinting in male rats have been more focused on partner preference and have demonstrated that this type of learned preference may depend on rewarding stimuli that the mother provides to the offspring during critical periods of life. For example, the positive effects of licking during the first 10 days of life can be conditioned to olfactory stimuli as well. In one study by Menard, Gelez, Coria-Avila, Jacubovich, and Pfaus (2006), newborn male pups were taken away from their mothers for 15 min every day. During this time away, males in a paired group were exposed to a lemon scent sprayed on the woodchip bedding of a different cage. At the same time, they received tactile stimulation performed artificially with a small paintbrush on their back and head, so that the strokes would mimic the dam's licking at the time that they smelled the lemon scent. Males in a control group were exposed to woodchip bedding sprayed with water alone during tactile stimulation. Both groups were weaned at 21 days of age and never exposed to the odor again. After 2 months, males were placed in a large open field ($123 \times 123 \times 46$ cm chamber) and allowed to copulate freely with two females at the same time, one scented and one unscented. The results of that preference test indicated that a significant proportion of the paired males displayed a preference to ejaculate first with the scented female, whereas the control group showed no preference for scented females (Menard et al., 2006).

Other experiments have demonstrated that imprinting is so powerful that it can actually induce sexual preferences toward a different species. In one study, for example, male sheep and goats that were cross fostered developed a sexual partner preference toward females of the species of the foster mother (Kendrick, Hinton, Atkins, Haupt, & Skinner, 1998). Taken together, these studies indicate that stimuli sensed during early development can be learned and consequently direct partner preference during future sexual encounters.

Juvenile period

Although the period of maternal care is very critical for development, the postweaning period is also important because animals will experience their first non-fraternal social interactions through play behavior. In rats, this behavior involves repeated bouts of rough and tumble play and dorsal contacts directed to the nape of the opponent (Panksepp, Jalowiec, DeEskinazi, & Bishop, 1985). Social play has positive effects on the normal development of animals and is also believed to be rewarding. For example, one study showed that socially isolated juvenile rats allowed to engage in intense bouts of rough and tumble play during short, daily periods, did not turn timid and aggressive, compared to isolated animals not allowed to play (Einon, Humphreys, Chivers, Field, & Naylor, 1981). Furthermore, young animals develop place preference only for sides associated with the possibility to engage in play behavior (Calcagnetti & Schechter, 1992). The rewarding properties of social play (as well as other social experiences) are modulated by opioids, since treatment with opioid agonists such as morphine increases the intensity and frequency of the behavior (Panksepp et al., 1985), whereas an opioid antagonist like naloxone readily reduces its frequency.

Very recently, a study from our laboratory showed that female rats develop conditioned partner preference toward males that bear olfactory cues previously associated with juvenile play (Paredes-Ramos, Miquel, Manzo, & Coria-Avila, 2011). In that study, prepubescent female rats were socially isolated at 31 days old and were allowed to play daily for 30 min, during 10 trials, with another young female that bore an odor (either almond or lemon scent) as a CS. One day after the last conditioning trial, all the females were tested for conditioned play partner preference with two young and prepubescent male rats, one scented with almond and the other with lemon. The results indicated that females in the almond-paired group preferred the almond male as play partner, ignoring the lemon-scented male. However, in the lemon-paired group, females preferred the lemon-scented male. Some days later, when females were approximately 55 days old, they were ovariectomized, and hormone-primed with estradiol and progesterone to induce sexual receptivity. Then, they were tested for their first sexual partner preference with two unfamiliar stud males, one almond-scented and one lemon-scented. The results indicated that females displayed a very selective sexual partner preference toward males bearing an odor (either almond or lemon) previously paired with juvenile play. This was observed with more solicitations, hops and darts, visits, and olfactory investigations, directed toward the preferred male. Sexual solicitations (including hops

and darts) indicate females sexual desire and function as an invitation for males to engage in sexual behavior with them (Pfaus, Shadiack, Van Soest, Tse, & Molinoff, 2004). Indeed, the females solicited more toward males bearing the conditioned stimulus, which resulted in more intromissions and ejaculations from them, including the very first ejaculation. This might have very important implications in gonadally intact females. For instance, we have previously demonstrated that the first ejaculation may result in 100% of fatherhood if the female does not receive any other intromission for at least 10 min after (Coria-Avila, Pfaus, Hernandez, Manzo, & Pacheco, 2004). Accordingly, conditioning of partner preference during the juvenile period may bias assortative mating.

Postpubertal period

The postpubertal period is more flexible in time than the early postnatal weeks and juvenile phase. It is a critical period because animals commonly experience their first sexually rewarding encounters. For example, in one study of male rats, the levels of luteinizing hormone and testosterone were increased following exposure to a conditioned odor (i.e. wintergreen) previously paired with copulation (Graham & Desjardins, 1980). The increases were similar to those following exposure to estrous odors in naïve males, suggesting that association with the copulatory reward state makes a neutral odor to become a CS capable of triggering a conditioned neuroendocrine response that prepares the animal for a sexual behavior.

Conditioned odors associated with copulation can also facilitate motivation for a partner. For example, Kippin, Talinakis, Chattmann, Bartholomew, and Pfaus (1998) trained one group of males (the paired group) to associate an almond or lemon odor painted on the back of a female's neck and anogenital region with copulation to ejaculation. Another group (the unpaired group) received copulatory trials with unscented females (Kippin et al., 1998). On a final test in a laboratory open field, the males received access to two sexually receptive females, one scented with the odor and the other unscented. Males in the paired group displayed a conditioned partner preference in which the scented females were chosen to receive the males' first ejaculation. Subsequent studies revealed that the learning of this conditioned ejaculatory preference took place during the postejaculatory refractory period (Kippin & Pfaus, 2001). Thus, polygamous male rats acquired a preferred partner by exposure to a simple Pavlovian conditioning procedure that linked a neutral olfactory stimulus to sexual reward induced by ejaculation.

Based on the fact that the postejaculatory period is sufficiently rewarding to support the development of heterosexual partner preference in male rats, we tested its effects on conditioned homosexual partner preference. In a study from our laboratory (Cibrian-Llanderal, Triana-Del Rio, Tecamachaltzi-Silvaran, & Coria-Avila, 2011), we allowed male rats to copulate to one ejaculation with sexually receptive female rats. Immediately after ejaculation, males were gently removed from the female's arena and were placed into a different arena to cohabitate for 1 h with another male that bore almond scent as a CS. This occurred during 10 conditioning trials, just as in the study of Kippin and Pfaus (2001). In a control group, males were placed for cohabitation 12 h after copulating with the female. One day after the last conditioning trial, males were tested for homosexual partner preference in a chamber with two stud males as potential partners, one almond scented and one unscented. Contrary to our hypothesis, both groups failed to develop a conditioned homosexual preference for the CS+ male, indicating that the 'critical period' induced by ejaculation is sufficient to support heterosexual, but not homosexual conditioning of partner preference in putatively heterosexual males. Nevertheless, there were some interesting statistical trends (non-significant). For example, about 40% of the males in the experimental group displayed mount attempts toward scented males, compared to 20% of males in the control group. In addition, experimental males displayed higher frequency of play behaviors (dorsal contacts and rough-and-tumble events) toward scented males. This might indicate that exposure to a male during the postejaculatory period resulted in conditioned play partner preference but not in homosexual preference.

Instrumental conditioning of partner preference

In sexually mature individuals, the first sexual experiences may facilitate the conditioning of partner preference via a combination of Pavlovian and instrumental (operant) learning. Instrumental learning describes a response-reinforcer contingency in which an animal learns to operate on its environment (Skinner, 1953, 1966). It occurs when an animal adapts its behavioral responses under particular schedules of reinforcement, circumstances that have been associated with the delivery of reward or punishment. Specifically, when an animal shows a response that is followed by sexual reward, the frequency of that response increases and its latency decreases. For example, female rats that pace copulation are more likely to experience sexual reward (Paredes & Alonso, 1997; Paredes & Vazquez, 1999). Therefore, females will solicit more frequently and with shorter latencies toward male partners that bear CS associated with the possibility to pace copulation (Coria-Avila et al., 2005, 2006). This is referred to as positive reinforcement. Conversely, when an animal's response is associated with punishment, the response is likely to diminish in frequency and increase in latency. For example, although tickling induced by hand is rewarding to juvenile female

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rats, it appears to be stressful in adults. Consequently, females will solicit less to a male partner that bears a CS associated with tickling, will spend less time with him, and will prefer any other novel available male (Paredes-Ramos et al., submitted). At the same time, preference for a novel male can be strengthened if, by choosing him, the female reduces the possibility to be tickled. This is referred to as negative reinforcement. In addition, if the female experiences reward with the novel male, then partner preference may be shaped through a combination of positive and negative reinforcement.

Accordingly, sexually experienced animals can display conditioned sexual motivation (*via* Pavlovian conditioning) or learn to perform a variety of tasks (*via* instrumental conditioning) in order to gain access to a partner, presumably because of the association with sexual reward (Pfaus, Kippin, & Centeno, 2001). It is believed that the capacity to experience reward during sexual behavior evolved to facilitate the likelihood of copulation. Therefore, from a psychological perspective, sex has rewarding properties because stimuli that predict copulation increase the probability of appetitive instrumental responses aimed at working for or approaching those stimuli. Such performance can indicate levels of sexual motivation triggered by the cues of the partner or can be used to infer partner preference if animals are allowed to choose between several potential conspecifics to copulate with (Pfaus et al., 2001).

First sexual experiences

As discussed before, the sexual reward state induced by ejaculation is a critical UCS that facilitates a subsequent preference for stimuli that predict it. It has been hypothesized that conditioned ejaculatory preference in rats may be a rudiment of the monogamous behavior observed in other species of rodents (Pfaus et al., 2001). For example, mating facilitates pair-bonding in monogamous prairie voles (Williams, Catania, & Carter, 1992), suggesting that mating-induced pair bonds are mediated by sexual reward (Young & Wang, 2004). Pair bonds are observed when a vole has the choice of two partners, one familiar, with whom copulation occurred previously, and one novel. A bonded vole usually selects the familiar one to spend more time, copulate, and reproduce with. Some reports indicate that this behavior may last for life, since bonded individuals rarely mate with other partners even following permanent separation from the original partner (Getz, McGuire, Pizzuto, Hofmann, & Frase, 1993). It is possible that a bonded vole remains monogamous because of the constant positive reinforcement from the partner during social contact and recurrent mating. As a result, the specific features of the partner (e.g. olfactory signature) may become conditionally preferred and reinforced by social stimulation and mating.

Other stimuli that affect partner preference conditioning

Stress

There are arousing stimuli other than those experienced during copulation that can also facilitate the formation of partner preference. For example, in male prairie voles, long periods of swimming are believed to be stressful. If voles are forced to swim and then allowed to cohabit for a period of 6 h (which is normally not enough time to induce bonding), pair bonds are more likely to occur (Carter, 1998; DeVries, DeVries, Taymans, & Carter, 1996). This behavior is believed to be facilitated via the hormones that are released during the stress response (i.e. corticosteroids), because injections of corticosterone in males facilitate the formation of pair bonds (DeVries et al., 1996). The exact process is not completely understood; however, one possible explanation is based on the fact that corticosteroids induce an increase of activity in mesolimbic dopamine (DA) (Der-Avakian et al., 2006; Rouge-Pont, Marinelli, Le Moal, Simon, & Piazza, 1995), and DA mediates the development of partner preferences and pair bonds (Aragona, Liu, Curtis, Stephan, & Wang, 2003; Aragona et al., 2006; Wang, et al., 1999). There is evidence in humans about the effects of stress on the formation of new pair bonds. Some cases have been documented in the so-called Stockholm syndrome (Julich, 2005; Namnyak et al., 2008), in which a hostage develops empathy or a bond toward the captor. Thus, it is possible that, depending on its intensity and duration, a stress response may facilitate or disrupt the formation of partner preferences. However, the exact mechanisms that result in preference or aversion are not well understood (Fig. 1).

Pharmacological manipulations

Dopamine

Normal sexual encounters that result in sexual reward are probably mediated by the dynamic interrelationship in the release of DA (Pfaus, et al., 1990; Pfaus, Damsma, Wenkstern, & Fibiger, 1995), opioids (Agmo & Berenfeld, 1990; Paredes & Vazquez, 1999; van Furth, Wolterink, & van Ree, 1995), oxytocin (OT), and vasopressin (Bales et al., 2007; Bielsky & Young, 2004; Carmichael et al., 1987; Carter, Williams, Witt, & Insel, 1992; Cushing & Carter, 2000; Young & Wang, 2004). These neurotransmitters modulate attention, prediction, expectation, reward, and trust, which are the emotional substrates for partner preference (Berridge & Robinson, 1998; Pfaus et al., 1990; Schultz, 2002; Schultz, Apicella, Scarnati, & Ljungberg, 1992; Tauber et al., 2011). It is also likely that any stimulus that affects the release of these neurotransmitters will affect the formation of partner preferences.

For example, manipulations of the dopaminergic system (DA) with antagonists disrupts the formation of partner preference in rats and voles; whereas a low doses

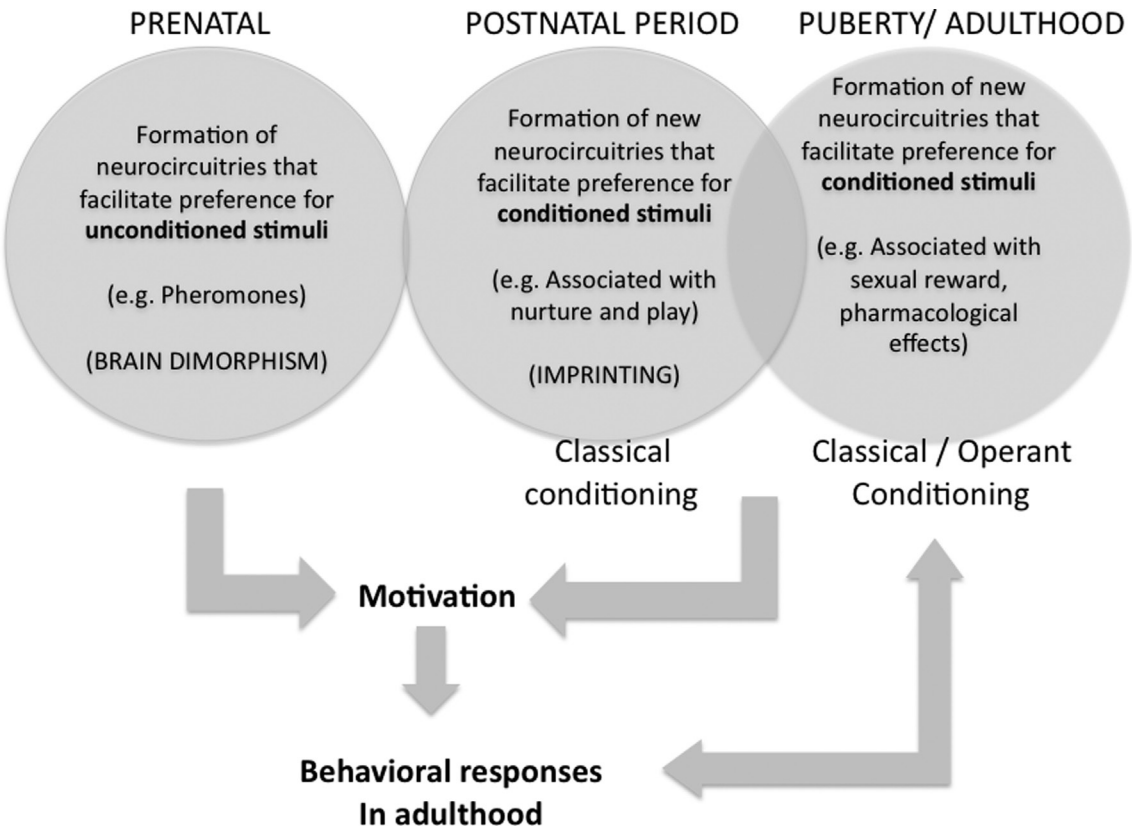

Fig. 1. Periods in which development of partner preference may occur. During the prenatal period, there is organization of brain circuitries (e.g. brain dimorphism) that facilitates motivation and preference for partners that bear strong UCS. This innate preference presumably needs no learning. However, a critical period of learning starts during the postnatal period. Animals associate CS with rewards experienced during that period. This association may facilitate phenomena such as imprinting. During puberty/adulthood, animals experience their first sexual encounters and continue to associate CS with UCS such as sexual reward (or other types of reward such as pharmacological). Both postnatal and puberty/adulthood periods may either strengthen or override brain circuitries organized during the prenatal period, and therefore affect motivation for a partner, and the behavioral responses indicative of preference. Modified with permission from Coria-Avila et al., 2010.

of DA agonist facilitate partner preference (Aragona et al., 2003; Coria-Avila et al., 2008a; Gingrich, Liu, Cascio, Wang, & Insel, 2000). It has been shown that D1- and D2-type receptor agonists play opposite roles in the formation of pair bonds in monogamous voles (Aragona et al., 2006). For instance, a D1 agonist or D2 antagonist blocks the formation of mating-induced pair bonds (Gingrich et al., 2000); but a D2 agonist will facilitate the formation of pair bonds if the treated vole cohabitates for few hours with a potential partner (Wang et al., 1999), similar to the preference that develops after mating.

Based on the fact that enhanced D2-type receptor activity facilitates the formation of heterosexual partner preference, we tested the effect of a D2 agonist, quinpirole, on the formation of conditioned homosexual preference. Thus, we treated a group of sexually naïve male and female rats with quinpirole and allowed them to cohabitate with a same-sex individual (cagemate) during 24 h, every 4 days, for a total of 3 trials (Triana-Del Rio et al., 2011). The cagemate was scented with almond odor as the CS, so that the rats treated with quinpirole would associate it with the UCS caused by the injection. In the control group, animals received only saline but were allowed to cohabitate with scented partners as well. Four days after the final conditioning trial, the rats were drug-free and tested for homosexual partner preference in a three-compartment chamber. In one compartment, there was the scented partner they cohabitated with, and in the other compartment, there was a novel partner of the same sex. The experimental rat was placed in the third compartment and was allowed to move freely between the compartments. The results showed that males, but not females, displayed a preference for the scented partner (of the same sex), as observed with more time spent together, more olfactory investigations, higher proportion of mounts between them, and more non-contact erections when were exposed to each other behind a wiremesh that prevented direct contact.

Aragona et al. have shown that D2-type receptor activity in the rostral shell of the nucleus accumbens (NAc) facilitates the formation of heterosexual partner preference in monogamous voles (Aragona et al., 2003,

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2006). Accordingly, it is likely that NAc D2-type receptor activity also modulates the formation of conditioned homosexual partner preferences in male rats and that repeated cohabitation under the pharmacological effects of quinpirole helped crystallize the preference for the male cagemate.

It has been also described that the proportion of D1 and D2 receptors in the brain is different between monogamous and polygamous rodents. D1-like receptors are more abundant in polygamous voles (Aragona et al., 2006), and it has been argued that they function to prevent bonding in a species in which polygamy is the reproductive strategy. However, several studies have shown that even polygamous rodents can learn to display partner preference after many conditioning trials (Coria-Avila et al., 2006; Ismail, Gelez, Lachapelle, & Pfaus, 2009; Kippin & Pfaus, 2001; Paredes-Ramos et al., 2011). Although they do not become monogamous, polygamous rats learn to prefer a specific partner because of the association with reward. It remains to be demonstrated to what extent repeated copulation (or cohabitation under the effects of quinpirole) upregulates D2-like receptors in a polygamous brain to facilitate partner preference conditioning.

Opioids

These are believed to be the main modulators of sexual reward (Agmo & Berenfeld, 1990; Coria-Avila et al., 2008b; Paredes & Alonso, 1997; Paredes & Martinez, 2001) since opioids blockade disrupts the formation of conditioned preferences induced by sex. They are mainly released in the medial preoptic area (MPOA) (van Furth, et al., 1995) and ventral tegmental area (VTA) (Balfour, Yu, & Coolen, 2004). At the MPOA, opioids facilitate reward (Garcia-Horsman, Agmo, & Paredes, 2008) and, at the VTA, produce disinhibition of mesolimbic DAergic neurons (Balfour et al., 2004; van Furth et al., 1995). A recent study showed that male rats treated with a single injection of 10 mg/kg of the opioid agonist morphine displayed a conditioned ejaculatory preference in later encounters for a female paired with the injection (Jones, Bozzini, & Pfaus, 2009). Such dose of morphine was high enough to disrupt copulation during the single conditioning trial. However, even in the absence of copulation, morphine may mimic the UCS that occurs during the postejaculatory period, facilitating the formation of heterosexual partner preference. It is unknown, whether or not treatment with morphine may facilitate the development of conditioned homosexual partner preference in rats. Furthermore, it has been reported that opioid receptors are found in the same proportion in monogamous and polygamous voles (Insel & Shapiro, 1992), which suggest that the experience of sexual reward during mating might be similar. Therefore, although opioids are required for conditioning partner preference, the formation of long-lasting preferences would depend on other neurochemicals, such as DA, OT, or vasopressin (AVP).

Other peptides

In the monogamous voles, females express more OT receptors in areas related to recognition and sex, compared to polygamous females (e.g. in prelimbic cortex, bed nucleus of the stria terminalis, dorsomedial thalamus, lateral amygdala, and NAc; Insel, 1992). However, polygamous females express more OT receptors in other areas such as the lateral septum, ventromedial hypothalamus, and corticomedial amygdala (Young et al., 1997). Only a few of these differences appear to be relevant in the formation of partner preferences. For instance, OT antagonist in the prelimbic cortex or NAc can block the formation of new partner preferences in voles induced by sex or D2 agonists (Liu & Wang, 2003). With regard to AVP, monogamous male voles express higher density in the ventral pallidum, compared to polygamous males (Lim & Young, 2004). Infusions of AVP antagonist into the ventral pallidum disrupts the development of pair bonds induced by sex (Young & Wang, 2004). There is a study indicating that the increase of AVP receptors *via* viral vectors from a monogamous to a polygamous male vole can readily increase the capacity of the latter to form pair bonds (Lim et al., 2004).

Given the systematic interrelationship between DA and some peptides like OT and AVP, we tested the effect of a D2-type receptor agonist+OT on the development of homosexual partner preference in female rats. As discussed above, the effect of a D2 agonist alone (quinpirole) during cohabitation, facilitated conditioned homosexual preference between male rats but not between female rats. However, as we found later, treatment with quinpirole, followed 10 min later by OT, facilitated the development of homosexual preferences between females in just three trials (Cibrian-Llanderal et al., submitted). The preference was observed with more proceptive behaviors (i.e. solicitations and hops and darts) and more time spent together with the familiar female. The effect of quinpirole+OT indicates that female rats not only require D2-type receptor activity but also the effects of the peptide to crystallize a preference for a partner. In fact, that combination may be required to experience sexual reward during mating and may reflect the combination of these two neurochemicals during rewarding copulation in which female receive intromissions (Becker, Rudick, & Jenkins, 2001; Coria-Avila et al., 2005, 2006) (Table 1).

Other implications of learned partner preferences

Inbreeding and outbreeding

It can be argued that constant preference for familial features in a mate should not be desirable, since it would

Table 1. Some unconditioned stimuli (UCS) that function as reinforcers and help condition partner preference in rodents. Some UCSs are explicitly sexual, but others are not. A partner that bears conditioned stimuli (CS) that predict the UCS will be preferred.? = no data are available

					Preference that is facilitated		
	UCS	Species	Sex	Effect on partner preference formation	Heterosexual	Homosexual	Reference
Non-sexual	Nurture	Rats	Males	Facilitation	Yes	?	Fillion & Blass, 1986; Menard et al., 2006
	Juvenile play	Rats	females	Facilitation	Yes	?	Paredes-Ramos et al., 2011
	Cohabitation	Voles	Both	Facilitation	Yes	No	Williams et al., 1992; Triana-Del Rio et al., 2011
	Tickling	Rats	Female	Devaluation	Yes	?	Paredes-Ramos et al., submitted
	Stress, cort	Voles	Males, females	Facilitation, blockade	Yes	?	DeVries et al., 1996
Sexual	Copulation	Rats, voles	Both	Facilitation	Yes	No	Williams et al., 1992; Young & Wang, 2004
	Ejaculation	Rats	Males	Facilitation	Yes	No	Kippin & Pfaus, 2001; Cibrian-Llanderal et al., 2011; Cibrian-Llanderal et al., submitted
	Paced copulation	Rats	Female	Facilitation	Yes	?	Coria-Avila et al., 2005, 2006
	Clitoral stimulation	Rats	Female	Facilitation	Yes	?	Parada, Abdul-Ahad, Censi, Sparks, & Pfaus, 2011
Pharmacological	D2 agonist	Rats, voles	Female	Facilitation	Yes	Yes	Wang et al., 1999; Cibrian-Llanderal et al., submitted; Triana-Del Rio et al., (2011)
	OT agonist	Voles	Female	Facilitation	Yes	Yes	Beery & Zucker, 2010
	D2 agonist + OT	Rats, voles	Female	Facilitation	Yes	Yes	Liu & Wang, 2003; Cibrian-Llanderal et al., submitted
	AVP	Voles	Males	Facilitation	Yes	?	Lim et al., 2004; Lim & Young, 2004

facilitate inbreeding. Continuous inbreeding may result in the phenotypic expression of unwanted genotypic information, which is passed on as recessive genes from generation to generation without being expressed, until two parents with similar genotypes reproduce. Accordingly, sexual imprinting should not be the best strategy to reproduce and animals should look for partners genetically different in order to avoid inbreeding.

Observations of the mating strategies in house mice indicate that they avoid mating with individuals that have a similar major histocompatibility complex (MHC). The MHC genes produce molecules that help the immune system distinguish organisms that are different and that could potentially cause diseases. A MHC that is more heterogeneous will have a broader range to recognize what is familiar or different. Consequently, the more different the genes from the parents, the more heterogeneous the MHC of the offspring, which results in a more capable immune system. It has been argued that animals should have systems that evolved to recognize and prefer potential mates with different MHC. That is, partner preference should be directed toward non-related individuals, rather than toward genetically similar partners that are potential carriers of unwanted genotype. There is evidence indicating that the natural tendency of mice to mate with partners of a different haplotype is not innate, since sexual preference can be reversed toward a partner of the same haplotype through imprinting. In one study, for example, male mice that were reared by a foster mother of a genetically different strain displayed a copulatory preference toward females of their own strain (Yamazaki et al., 1988), which may suggest that the relatives were not recognized as familial and, therefore, were preferred as mates.

Learning to recognize familial odors would indicate to an animal its family identity and, therefore, would help to avoid mating with them (potentially carrying similar genes). In one study, it was showed that mice can recognize MHC of other individuals through olfactory signals and that such olfactory recognition is learned through imprinting in early periods of life. In the study, they cross-fostered female mice pups with mothers that had different MHC genes. When the pups became adults, partner preference was tested toward individuals with similar MHC or with MHC genes of the foster family (Penn & Potts, 1998). Similar to the results of Yamazaki et al. (1988), Penn and Potts showed that females avoided mating with males carrying MHC genes similar to the foster family, which supported the hypothesis that MHC-dependent familial imprinting provides a mechanism for avoiding inbreeding.

Bateson (1978) suggested that sexual imprinting facilitates the best possible outbreeding and prevents animals from inbreeding. His statement was based on a series of mate-choice experiments with Japanese quails. He demonstrated that males showed the highest rates of approach and copulation with females whose coloration was slightly different from that of the foster mother, relative to females with the exact coloration (Batenson, 1978). This has lead to the suggestion that, as a result of imprinting, mate choice is directed toward a partner that bear cues that are slightly unfamiliar, which is evaluated based on familiar memories consolidated during early and critical periods of life. Accordingly, imprinting may facilitate preference toward an individual that is slightly different to guarantee outbreeding, and at the same time, it guarantees breeding with an individual that is familiar and probably equally adapted to the environmental circumstances.

About learned homosexual partner preference in humans

Our findings indicate that rats can develop conditioned homosexual partner preferences during adulthood. For this to occur, males need to cohabitate during enhanced D2-type activity, whereas females need D2+OT enhanced activity. It is unknown to what extent this phenomenon extends to humans and must be interpreted with caution. Some drugs such as cocaine or amphetamine can indeed enhance DA activity in humans, but they do not act directly on D2-type receptors but rather on all DA receptors. This includes D1-type, which activation prevents the development of new pair bonds in voles. In fact, it has been shown that male voles that receive chronic amphetamine fail to form mating-induced pair bonds, probably because a drug-induced up regulation of D1-type receptors (Liu et al., 2010).

The development of conditioned homosexual partner preference facilitated by DA and OT agonists might not be a phenomenon that easily occurs in nature. In fact, it may occur only under laboratory conditions. Nevertheless, such findings suggest that the adult neurocircuitries that direct partner preferences are not fixed or hardwired but rather flexible and adaptable to the new contingencies that an organism encounters.

Conclusions

Stimuli that predict strong rewards will induce responses that prepare the animal to obtain them. Partner preference that occurs toward a novel individual may be the unconditional result of the UCS-UCR association or may also represent the result of learning and the CS-CR association. Rewards associated with the early postnatal weeks, nurture, juvenile period or first sexual experiences can readily facilitate the formation of heterosexual partner preference in various species of rodents and probably in humans too. Based on the rodent data, it is also possible that some rewarding associations with same-sex individuals facilitate same-sex partner preference, but this has not been demonstrated in humans. In this respect, finding common brain regions and neurochemical or endocrine

systems activated in monogamous and polygamous species and in those with heterosexual or homosexual partner preference should have a profound impact on our understanding of diversity in mate choice and mate strategies. Evolutionary biologists and psychologists must take into consideration the idea that an individual's experience with reward (i.e. sexual and pharmacological) can override presumably 'innate' mate choices (e.g. assortativeness) or mate strategies (e.g. monogamy or polygamy) by means of Pavlovian and operant contingencies. In fact, it is also innate (and perhaps even more fundamental) to learn about the environment in ways that maximize reward and minimize aversive outcomes, making so-called 'proximate' causes (e.g. pleasure) ultimately more powerful predictors of social behavior and choice than so-called 'ultimate' causes (e.g. genetic or reproductive fitness).

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