The nose knows: MHC-dependent mate selection in humans through odor preference

Alexandra Roman
Department of Biology
Lake Forest College
Lake Forest, Illinois 60045

Abstract

Mate selection is a key determinant in an organism's fitness. In humans, there are significant cultural and social factors at play in selecting a partner; however, biological and genetic factors tend to be overlooked. Recent studies have shown that humans possess a preference for partners that is dependent on the major histocompatibility complex (MHC) (Wedekind et al., 1995). MHC molecules' primary function is in the immune system to present foreign antigens to T-cells. This diverse set of proteins are encoded by alleles to help protect against a range of parasites. Hypotheses that explain the diversity of MHC alleles in human populations include overdominance, rare alleles, and inbreeding avoidance; however, this diversity is thought to also be maintained by sexual selection. Mate selection on the basis of MHC-dependent odor has been demonstrated in non-human animal systems, such as mice, where dissimilar MHC types are preferred in mates. However, support for MHC-dependent mate selection in humans is less well-established, as a number of studies attempting to evaluate this issue report conflicting results. This review evaluates the research that has been conducted thus far on MHC-dependent odor preferences in human mate selection. The goals of this review are to critically summarize the results of this set of studies, determine whether they provide additional evidence for the three hypotheses

Introduction

The major histocompatibility complex (MHC) is an important set of proteins involved in immune response. Both MHC class I and class II loci present foreign antigens to T-cells. In order to perform this function, each MHC molecule is able to recognize and bind a wide range of specific peptide sequences (Wooldridge et al., 2012). This polymorphic quality aids MHC's ability to recognize a wide variety of antigens, as well as "self" versus "non-self" proteins (Klein, 1986). Additionally, there are many different alleles that have been identified at each MHC gene location, with some loci known to have upwards of 2,000 variants (Trowsdale & Knight, 2013). It is unclear as to how these many different alleles arose in the genome and were maintained by selection. There are three major hypotheses to provide some explanation for this polymorphic nature of MHC: overdominance, rare alleles, and inbreeding avoidance.

The overdominance hypothesis suggests that individuals who are heterozygous specifically at MHC loci are better able to recognize a larger amount of pathogens due to their codominant expression (Eggert et al., 1998). This gives these individuals an enhanced immune response, thus increasing their overall fitness (Doherty & Zinkernagel, 1975). The crux of this argument is that heterozygotes must be fitter than either homozygote – the dominant allele by itself cannot provide the selective advantage (Piertney & Oliver, 2014). Additionally, heterozygote MHC genotypes must retain equal fitness benefits regardless of the nature of the heterozygosity in order for this hypothesis to be correct (De Boer et al., 2004).

A second hypothesis as to how this MHC gene diversity is maintained is known as the rare allele hypothesis. If an organism possesses a rare allele that no pathogen is adapted to, this organism is less susceptible to infection. This translates to a fitness advantage and this rare allele will become more common. However, parasites in the environment will be under stronger selection to circumvent this adaptation, and the strength of selection will increase as the allele becomes more common. Once one of these pathogens evolve an adaptation that is able to infect organisms that possess this now common allele, the allele will decrease once again in proportion. This frequency-dependent selection repeats every time a new allele is generated that can respond to this pathogen (Piertney & Oliver, 2014). The rare alleles generated in these situations are not lost to drift; while they never become fixed in the population, they are neither eliminated (Slade & McCallum, 1992). This rare allele advantage is not mutually exclusive from the overdominance hypothesis, as their presence in a genome would meet criteria for both models to be true (Apanius et al., 1997).

A third hypothesis that explains MHC polymorphism is known as the inbreeding avoidance hypothesis. Inbreeding increases the chances of deleterious mutations becoming homozygous (Charlesworth & Charlesworth, 1987). One reason sex is thought to have evolved is to increase genetic diversity; consequently, the same selective pressures that maintain sex should maintain other mechanisms for inbreeding avoidance. Therefore, selection on mechanisms to recognize relatedness may be selected for. MHC gene diversity can serve as this indicator of relatedness. If two individuals share MHC alleles, they have a greater chance of being related. (Penn & Potts, 1999). Animal systems can use this information to avoid mating with close relatives.

Inbreeding avoidance is not exclusive from the disease resistance hypotheses of overdominance and rare alleles; a combination of the three may be employed in natural populations. Different mechanisms of selection can also take over when populations are under different circumstances (Penn & Potts, 1999). These modes of selection reward organisms that successfully select mates and produce offspring with increased fitness; thus, the diversity of MHC molecules in animals may be maintained by mate selection through disassortative mating (Winternitz et al., 2013).

A significant amount of animals select mates based on MHC gene dissimilarity. Congenic mice only differing in their H-2 type (equivalent of MHC in mice) were found to mate with individuals of a dissimilar H-2 type (Yamazaki et al., 1976). Female sticklebacks were found to utilize MHC peptide ligands in order to determine mate quality (Milinski et al., 2005). The Savannah sparrow will produce more extra-pair young in her brood if she is especially similar in MHC to her social mate. She will actively seek out MHC-dissimilar males for these extra-pair copulations (Freeman-Gallant et al., 2003). Finally, grey mouse lemurs also show a higher degree of heterozygosity and number of different MHC-types between mates when compared to random mating (Schwensow et al., 2008). Because the presence of MHC-dependent mate selection is found across different taxa, including primates, the question remains whether this mate selection is also present in humans.

Another important factor in MHC-dependent disassortative mating is how MHC molecules act as an indicator for animals to actively select optimal mates. One of the most powerful ways is through odor detection. Evidence suggests that congenic mice differing in MHC-type can be detected by other mice through odor (Yamazaki et al., 1983). It is still unclear how exactly MHC molecules generate specific odor profiles. Several proposed mechanisms include binding of odor molecules to MHC receptors, bacterial colonizing and coexpression of odor-producing genes that lie in the MHC region (Eggert et al., 1998). Further evaluation of these processes are beyond the scope of this review; for more information, see Hamid, 2016.

In this review, I will evaluate the results of each human study regarding MHC-type odor preferences in order to assess the current evidence for disassortative MHC-dependent mate selection. In addition, I will examine whether these studies support any of the three hypotheses explaining MHC polymorphism (overdominance, rare alleles, inbreeding avoidance). I will also discuss the experimental design of each study and recommend future considerations for scientists interested in furthering research on MHC-dependent odor preferences in humans.

MHC-dependent odor detection in humans

Humans are able to detect MHC-dependent odors. Gilbert and colleagues (1986) used congenic mice strains that differed only in their MHC-type, and asked human participants to distinguish between whole-body, fecal pellet, and urine odors of two different strains. It was found that humans were able to discern differences between mice of different MHC-types through whole-body odor, female fecal pellets, and urine odors of two different strains. Humans were unable to distinguish between the fecal pellet odors of different male MHC-types, which may be due to the overall intensity of male odors versus female odors. This study demonstrates that humans have the ability to distinguish between different mouse MHC-types through odor perception, and that it likely translates to distinguishing between human MHC-types.

Humans also produce MHC-dependent odors. Ferstl and colleagues (1992) demonstrated that trained rats are able to discriminate between urine samples of humans with different MHC-types. This result

shows that humans also produce certain chemosensory signals in their excretions which are based on MHC genotype. This means that information regarding MHC diversity could be detected and used by another human. These critical findings serve as the basis for the investigation of MHC-dependent odor preferences in humans and the role they play in behavior. Even though these lines of evidence are cross-species (human and rodent), the highly controlled nature of the experiments through laboratory rodents provide insight into the capacity for human odor detection and production.

MHC-dependent odor preferences in human mate selection

Preliminary evaluation of MHC-dependent odor preferences for mate selection

The first study to examine MHC-dependent mate selection in humans was Wedekind et al. (1995). In this study, Wedekind and colleagues experimentally tested whether human female odor preferences for male body odor are dependent upon MHC genetic similarity. In this study, students were typed for HLA (human version of MHC) –A, –B, and –DR antigens. To donate their scent, men were given a white cotton T-shirt to sleep in for two nights and were asked to abstain from odor-producing foods, detergents, deodorants, and activities. Women were given a regenerative nose spray to use every day two weeks before the experiment, the novel Das Parfum by P. Süskind, and were tested in the second week of their menstrual cycle. Women who were taking oral contraceptives (the "Pill") were identified to account for additional confounding factors.

Each female scored six male subjects on a 0-10 scale for pleasantness, and each male subject was evaluated by two females (one of both a dissimilar and similar MHC-type). Their study found that women preferred the scent of males who were more dissimilar in MHC compared to the scent of males that were more similar. An additional finding showed that when women were taking oral contraceptives, their preferences reversed towards men with similar MHC backgrounds. Women also reported that men with more dissimilar MHC-types were reminiscent of current and past mates, suggesting that MHC-dependent odor preferences might be used in natural human mate selection. Wedekind et al. (1995) interpreted these findings to mean that human females use MHC-type in order to find dissimilar mates. Because oral contraceptives simulate pregnancy within a woman, Wedekind et al. also speculated this was due to women seeking kin, although this was not confirmed by their research design.

Although the Wedekind et al. (1995) was elegant, there was significant controversy within the scientific community after its results were published. Hedrick and Loeschcke (1996) expressed concerns through a direct correspondence regarding the sensitization of females to the odor detection task as well as the odor-neutrality restrictions on men. They argue that because of this study design, their findings are not generalizable to natural human mate selection. Wedekind and Seebeck (1996) reply to these concerns by stating their aim was to remove all confounding variables in order to test whether MHC specifically influences odor and odor preference in humans. Another concern posed by Hendrick and Loeschcke (1996) regarded the between-subjects study design and small sample size of women using oral contraceptives. Roberts et al. (2008) respond to this concern by conducting a within-subjects design in their study. Ever since Wedekind et al. (1995), an additional seven studies, including Roberts et al. (2008), examine the role of MHC and odor preference in humans. Each present conflicting results. This fuels the controversy surrounding Wedekind et al.'s initial findings, and requires a closer evaluation to determine which results and methods are consistent.

Replication of MHC-dependent odor preferences on mate selection

Wedekind and Füri performed a follow up study (1997) where the replication of their previous findings with a different experimental design and sample was a secondary aim. Within this study, they only used two females and four males as odor donors and correlated their MHC similarity to the smellers (121 male and female participants). Smellers were divided by their gender; females were divided whether they were taking oral contraceptives. The t-shirt wearer protocols of living odor-neutral, as well as HLA-typing of three loci for all participants were the same as Wedekind et al. (1995). Participants smelled all shirts, including those of the same sex, and scored them upon pleasantness; researchers did not take sexual orientation of smellers into account for this study at any time. This study was able to replicate the finding that females who were not taking oral contraceptives prefer dissimilar MHC-types. Memory associations regarding dissimilar MHC-dependent odors were also reminiscent of a past or current mate in both males and females. Finally, the study found that men preferred the odor of dissimilar MHC-types. The researchers were unable to find a significant correlation of females preferring similar MHC-types when on the Pill.

A total of three additional studies (Thornhill et al., 2003; Santos et al., 2005; Roberts et al., 2008) were released after Wedekind et al. (1995) and Wedekind and Füri (1997) that did not contain any of the scientists on these initial studies; this removed any potential bias that Wedekind might have had on the results. Unfortunately, the only other study that was able to replicate any result from either Wedekind et al. (1995) or Wedekind and Füri (1997) was Thornhill et al. (2003), which found that men preferred the odors of MHC-dissimilar women. In conclusion, no other study after Wedekind & Füri (1997) was able to replicate the finding that 1) women prefer MHC-dissimilar male body odors, and 2) the Pill reverses this effect. A fourth study performed by Jacob et al. (2002) did not directly evaluate whether females preferred dissimilar MHC-types in their mate choices; while they collected the relevant data, they did not perform analyses to answer this particular question. It may be of interest for a secondary analysis to be conducted using this data.

All three subsequent studies (Thornhill et al., 2003; Santos et al., 2005; Roberts et al., 2008) were similar in design to the first two studies (Wedekind et al., 1995; Wedekind & Füri, 1997) with slight alterations. Thornhill et al. (2003) excluded women taking oral contraceptives and did not test women according to their menstrual cycle; instead, researchers used calculations to estimate each participant's probability of conception after sex based on the day of their cycle. Santos et al. (2005) included women on the Pill, but did not differentiate between them in the analyses; they also did not test women according to their cycle. Santos et al. (2005) also did not use T-shirts to collect odor; instead, male and female participants donated urine samples and sweat samples using a cotton sachet necklace which collected sweat from the sternum rather than the axillary region. Roberts et al. (2008) used a longitudinal study design, which was able to test Pill-user preferences before and after using oral contraceptives for three months. They used frozen shirts instead of fresh shirts, and also presented half of each shirt to a smeller at a time, potentially reducing odor detectability. Finally, both studies involving Wedekind (1995, 1997) contained ethnically homogenous populations; the other three studies had a more diverse sample of participants.

While the effects of the different study designs are unclear, it is possible that they were strong enough to reduce the power of the results done to levels of non-significance; however, it may also be indicative that the skepticism surrounding Wedekind and colleagues' (1995) original results is well founded. Because nearly 10 years has passed since Roberts et al. (2008) directly examined MHC-dependent odor preferences in human mate selection, perhaps a replication by a different scientific group is in order, with certain considerations kept in mind (see 'Future considerations in study design').

Ancillary results in MHC-dependent odor preference research

Evidence for overdominance hypothesis

The primary aim of Wedekind & Füri (1997) was to determine whether MHC-dependent odor preferences lead to general MHC heterozygosity or specific allele combinations. Their results found that there were no preferences for specific allele combinations within the study population. Participants only preferred odors based on dissimilarity alone, which would result in a greater heterozygosity in offspring. However, this may be due to the context in which the population was tested; additional trials should be conducted in regions that are under stronger selection for disease resistance, as this population may have been "too healthy" to prefer specific allele combinations (Wedekind & Füri, 1997; Penn & Potts, 1999).

Evidence for determining paternity

Jacob and colleagues' (2002) primarily tested whether females use inherited MHC allele information or exposure to their parental MHC type in order to select mates based on MHC-dependent odor. Because researchers conducted the study within an isolated community, they had information regarding the parental generation of the sample. Unmarried females who had never been pregnant and were menstruating were selected from the community, while six diverse male odor donors were from the outside. Their study design asked women to smell all six male odors and choose their most preferred and least preferred; this is significant because ratings of pleasantness ("liking") and actual mate choice ("wanting") are enacted by different neural pathways (Berridge & Robinson, 1998).

Women were found to select males that were more similar to their paternally inherited alleles of their MHC-type, whereas males who were less similar were selected less often (Jacob et al., 2002). Maternally inherited alleles, as well as exposure to non-inherited alleles from either parent, were not a factor in this selection. This is the only study to demonstrate that mate choice based on MHC-preferences are determined by paternity. Additionally, Wedekind & Füri (1997) and Thornhill et al. (2003) found that men prefer dissimilar MHC-dependent odors in females. These three results may be due to paternity detection. Theoretically, if men share fewer MHC alleles with their female mate, they could more reliably detect their own alleles in offspring to ensure their parentage (Thornhill et al., 2003). Females selecting for paternally inherited alleles in mates might help mask paternity of their offspring in extra-pair copulations. Additionally, MHC detection could act as a mechanism for kin selection to identify paternal kin in promiscuous species, such as baboons, and bias social behaviors towards them (Smith et al., 2003).

Evidence for optimal versus maximal dissimilarity

Because Jacob et al. (2002) found a selection bias for males that share paternally inherited alleles, this might indicate a preference for greater MHC-similarity rather than MHC-dissimilarity. However, a closer look at the study design demonstrates that this is not the case. Jacob et al. (2002) used HLA-typing for a total of 5 loci (the most in any study on human MHC-dependent odor preference so far). A total of 10 matches were theoretically possible, with 7 matches possible between participants. A female's most preferred choice shared two alleles on average, whereas a female's least preferred choice shared approximately one allele. Instead of supporting the hypothesis for maximal dissimilarity (where we would expect to see a female choose the least similar MHC-type to her own), we see a trend towards optimality.

This optimality has been demonstrated in both fish and mice (Milinski et al., 2005; Gilder & Slater, 1978). In sticklebacks, females are able to detect a male's MHC diversity based on peptide fragments shed in the water. Males with a suboptimal MHC diversity that are supplemented with additional peptides are deemed more attractive by females, whereas supplementation of a superoptimal male's peptides decreases his attractiveness. (Milinski et al., 2005). It has also been demonstrated that mice have a preference for slightly unfamiliar scents, which may have developed to avoid inbreeding; an aversion to very unfamiliar scents may also help to avoid interspecific hybridization or the dissociation of co-adapted gene complexes that provide a synergistic advantage (Gilder & Slater, 1978). Thus, there is some evidence for an optimal number of MHC diversity – this may help explain why results are insignificant when a correlation analysis is performed in human studies of MHC-dependent odor preferences.

Evidence for extra-pair copulations

Roberts et al. (2008) was unable to find significant results regarding MHC-dependent odor preferences in women (on or off the Pill); however, they reported a significant finding within their data stating that women in relationships prefer MHC-dissimilar male odors, whereas single women have MHC-similar odor preferences. While this explanation might be a reach on behalf of the author, it may show evidence of paired females seeking to increase offspring heterozygosity through extra-pair copulations. Evidence of this phenomenon has been demonstrated most clearly in birds (Freeman-Gallant et al., 2003, Richardson). MHC-similarity between Savannah sparrow pair bonds predicted female fidelity, such that there were more extra-pair young in broods where the female shared more MHC alleles with her mate (Freeman-Gallant et al., 2003). In order to clearly demonstrate this within a human population, information regarding the female's mate and offspring's paternity would have to be known.

MHC-dependent odor preferences for self-identification and advertisement

MHC odor preferences can be altered depending on the context (Penn & Potts, 1999); this is most clearly demonstrated in two studies regarding self MHC-dependent odor preferences (Milinski & Wedekind, 2001; Milinski et al., 2013). Although Wedekind et al. (1995) initially cited that perfumes might interfere with MHC-dependent odor detection, Milinski & Wedekind (2001) demonstrated that a human's perfume ingredient preferences are actually correlated with their own MHC genotype. Given that pleasantness scores of ingredients tested over two years remained consistent, this adds strength to the statement that these preferences are linked to an individual's MHC alleles. Perfume use may have evolved as an adaptive behavior in humans to advertise their MHC type to potential mates by amplifying their signal. The fact that no correlation was observed for ingredients that individuals would prefer on a mate might have to do with context (perfume is traditionally selected for use on self) or support for heterozygosity. Preference for an ingredient wouldn't be heightened if it was simply correlated to a specific allele. Instead, preference is heightened for many different alleles, which the correlation is unable to detect.

Milinski et al.'s (2013) study is the latest in the body of research on MHC-dependent odor preference, and it will likely guide what the future of this research looks like. Females were typed for their HLA-A and –B alleles, and then given two bottles which contained peptide solutions that contained the two most commonly observed HLA-A alleles in the sample. They were also given an untreated cotton shirt and odor-free soap for use before the experiment. Participants were instructed to put on the shirt, dispense four drops of one bottle's contents into their hand, and rub it under a particular armpit. They repeated this series of steps with the other bottle's contents. They were then asked to sniff each armpit, and fill out a questionnaire stating which armpit they preferred, as well as how strong the difference was between the two scents. They repeated these trials two to six times, making sure to use different sides, and were also asked whether they had a cold, smoked, or used contraceptives. Additionally, an fMRI study was also performed where participants smelled a self peptide solution, non-self peptide solution, solvent control, and peach odor control. Only females with normal olfaction and brain function were included in the study.

The results of this study showed a significant preference for the MHC peptide solution that matched their genotype; this difference was only observed once participants who smoked regularly or had a cold during the session were removed from the sample. This results shows that mate choice may be impaired by behaviors such as smoking. Additionally, fMRI results showed that the self peptide solution caused the right middle frontal cortex to activate; these brain regions are involved in cognitive self-recognition, and are separately from olfactory structures (Murphy et al., 2010). This result demonstrates that MHC peptides which cause body odor are used for self-identification, and may also be used to identify and avoid similarities in mates. Both Milinski & Wedekind (2001) and Milinski et al. (2013) studies still require replication, to remove any bias lead author Milinski might have on the results.

Future considerations in study design

Menstrual cycle

Previous studies have shown that women are more sensitive to detecting androstenol and other related chemicals near the peak of ovulation, where they are most fertile (Doty, 1981). Several studies tested female participants during their second week of their menstrual cycle (Wedekind et al., 1995; Wedekind & Füri, 1997; Roberts et al., 2008), whereas other studies did not take this factor into account (Jacob et al., 2002; Santos et al., 2005). Thornhill et al. (2003) did not test female participants near ovulation, but they did calculate their fertility based on where they were in the cycle, and found that men preferred the scent of women with a higher fertility status (more likely to conceive after copulation) over women of a lower fertility status. This has the potential to confound results; not only are women not being tested during their peak sensitivity to odor and pheromone detection, but men might also be preferring odors that are not MHC-related. In future studies, all trials using female participants (regardless if they are acting as odor donors or smellers) should be tested during the second week of their menstrual cycle, to control for these potential effects.

Odor sensitivity

Milinski et al. (2013) excluded participants that reported having a cold or regularly smoking from data analysis, due to their impaired olfaction (Frye et al., 1990; Hummel et al., 1998). This was an element that was not taken into account in any previous studies on MHC-dependent odor detection in humans. The impaired olfaction of an individual who has a cold or smokes could seriously reduce their ability to differentiate between MHC genotypes in themselves or other individuals, and could explain the lack of significance observed in previous studies. It also might explain why Wedekind et al. (1995) were able to find such significant results – because they asked participants to use the regenerative nasal spray in the two weeks prior to the trial, this may have aided any individuals with olfactory impairment to recover their abilities and perform in the study. For any future studies, all participants should undergo an evaluation to ensure normal olfaction. Any individuals that might have a decreased sense of smell, such

as smokers, should be removed from analysis.

Methods of odor collection

Roberts et al. (2008) and Jacob et al. (2002) froze shirt samples before participants smelled them in trials; the effects for freezing were tested and showed little difference after three months of storage compared to fresh shirts (Roberts et al., 2008). Roberts et al. (2008) also halved shirt samples, which may have reduced odor potency compared to presenting whole shirt samples. In most studies, whole shirt samples were presented fresh to participants, and this should be continued for future study methods.

Santos et al. (2005) used a sachet necklace of absorbent cotton to collect sweat samples from the sternum, which is an area with high perspiration. This was a strange methodological decision, as the axillary regions are an ideal location for odor dispersion; they typically perspire first, contain a large concentration of apocrine and sweat glands, and disperse the odor further due to the hair within the region (Mostafa et al, 2012). Santos et al. (2005) also used urine samples to test odor preferences. Although Gilbert et al. (1986) demonstrated that humans were able to distinguish between urine samples of congenic mice using MHC detection, humans are unlikely to use urine odor to size up potential mates. Future studies should continue using the axillary region to collect odor samples.

The use of supplemental MHC peptide solutions in Milinski et al. (2013) also provides new avenues for improved research design. Controls can be greatly improved by using particular combinations of peptides to uncover what degree of MHC similarity is preferred by humans. This way, other factors in odor besides MHC genotype are unable to confound the results. Additionally, natural human odors can be supplemented with MHC peptides in order to test whether they become more or less attractive to the smeller. Future studies should take advantage of this new method, in order to clarify previously ambiguous results.

Improving power of statistical analyses

There are several methods that can be used to increase the power of results. For instance, increasing the number of HLA loci typed can greatly increase accuracy and detection of dissimilarity between pairs. Jacob et al. (2002) typed the most (five) loci of all the studies. Santos et al. (2005) only typed two different alleles and cited this as a potential confound for not finding significant results, as loci that were unidentified may have affected the degree of similarity. Additionally, asking similar research questions will increase the congruency of the results. Jacob and colleauges' (2002) study design found that females choose mates with an optimal level of MHC dissimilarity – asking questions of this kind to see if results were obscured in Thornhill et al. (2003), Santos et al. (2005), and Roberts et al. (2008), while also reporting whether MHC dissimilarity was preferred (not "wanted") in the Jacob et al. (2002) study, the mechanism behind MHC-dependent odor preferences in humans might be clarified. Finally, it is important that all studies use a scale for rating pleasantness rather than a yes or no answer (Santos et al., 2005) and balance odor donors across smellers of different similarities to control for individual differences (Roberts et al., 2008), as this gives the data more statistical power for analysis.

Context

Different study populations operate under different modes of MHC diversity selection (Penn & Potts, 1999). Mechanisms such as inbreeding avoidance or disease resistance may be stronger in different environments. Thus, populations from different geographic regions may show preferences for different degrees of MHC similarity. This may explain why Wedekind et al. (1995), Wedekind & Füri (1997), and Jacob et al. (2002) found significant results through their ethnically homogenous populations, while Thornhill et al. (2003), Santos et al. (2005), and Roberts et al. (2008) did not. Asking participants to choose an odor over preference ratings might unveil other factors that influence MHC-dependent mate selection (Jacob et al., 2002). Genetic studies regarding MHC and mate pairs in humans located in different geographic populations demonstrate the importance of context; for more information, see Mercier (2016).

Implications of MHC-dependent selection in humans

The biological and genetic phenomena that affect mate selection has great consequences for human pair bonds and their reproductive success. Couples who share a significant amount of MHC alleles have a greater difficulty becoming pregnant through unprotected intercourse, greater difficulty achieving viable pregnancies using assisted reproductive technologies, greater likelihood to suffer from recurrent spontaneous abortions, and a greater likelihood to give birth to newborns with a reduced birth mass (Ober et al., 1992; Weckstein et al., 1991; Reznikoff-Etievant et al., 1991). Studies in birds (Freeman-Gallant et al., 2003; Richardson et al., 2005) may also translate in humans; a high degree of MHC-similarity may destabilize the traditional monogamous pair bonds in humans. This could result in females and males engaging in extra-pair copulations, as well as males being cuckholded, decreasing his overall fitness. Thus, any behaviors that may alter olfaction, such as taking oral contraceptives or smoking, may have unintended consequences on beginning a family and relationship satisfaction.

Conclusion

MHC-dependent mate selection is a fascinating research area that demonstrates how humans are able to detect favorable gene combinations in potential mates through olfaction. MHC composition is an important factor to be considered in a mate, as they have great consequences in regards to reproduction success and pair bond stability. While there have been several studies published that have attempted to elucidate the mechanism by which humans make these selections, their results are incongruent with one another. Because the study methods differ significantly from one another in several aspects, I have made several recommendations based on current findings in order to guide future studies. By further standardizing the odor preference protocol in humans, perhaps the optimal level of MHC similarity between mates can be determined. This information can inform the public on how much the nose knows, and how biological factors such as smell and genetics are more important than previously thought when it comes to mate selection in humans.

Note: Eukaryon is published by undergraduates at Lake Forest College, who are solely responsible for its content. The views expressed in *Eukaryon* do not necessarily reflect those of the College.

References

Apanius, V., Penn, D., Slev, P. R., Ruff, L. R., & Potts, W. K. (1997). The nature of selection on the major histocompatibility complex. Critical Review in Immunology, 17(3), 179-224.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Research Reviews, 28(3), 309-369.

Charlesworth, D., & Charlesworth, B. (1987). Inbreeding depression and its evolutionary consequences. Annual Review of Ecology and Systemicatics, 18, 237-268.

De Boer, R. J., Borghans, J. A., van Boren, M., Kesmir, C., & Weissing, F. J. (2004). Heterozygote advantage fails to explain the high degree of polymorphism of the MHC. Immunogenetics, 55(11), 725-731.

Doherty, P. C., & Zinkernagel, R. M. (1975). Enhanced immunological surveillance in mice heterozygous at the H-2 gene complex. Nature, 256, 50-52.

Doty, R. L. (1981). Olfactory communications in humans. Chemical Senses, 6, 351-376.

Eggert, F., Müller-Ruchholtz, W., & Ferstl, R. (1998) Olfactory cues associated with the major histocompatibility complex. Genetica, 104(3), 191-197.

Ferstl, R., Eggert, F., & Müller-Ruchholtz, W. (1998). Major histocompatibility complex-associated odours. Nephrology Dialysis Transplantation, 13, 1117-1119.

Freeman-Gallant, C. R., Meguerdichian, M., Wheelwright, N. T., & Sollecito, S. V. (2003). Social pairing and female mating fidelity predicted by restriction fragment length polymorphism similarity at the major histocompatibility complex in a songbird. Molecular Ecology, 12(11), 3077-3083.

Frye, R. E., Schwartz, B. S., & Doty, R. L. (1990). Dose-related effects

of cigarette smoking on olfactory function. The Journal of the American Medical Association, 263(9), 1233-1236.

Gilbert, A. N., Yamazaki, K., Beauchamp, G. K., & Thomas, L. (1986). Olfactory discrimination of mouse strains (Mus musculus) and major histocompatibility types by humans (Homo sapiens). Journal of Comparative Psychology, 100(3), 262-265.

Gilder, P. M., & Slater, P. J. B. (1978). Interest of mice in conspecific male odours is influences by degree of kinship. Nature, 274, 364-365.

Hamid, K. (2016). Piecing the puzzles together: Understanding MHC related molecular pathways in organisms' olfactory systems to achieve reproductive success. In A. W. Shingleton (Ed.), NEUR482: Senior Seminar: Sex and Evolution (Vol. 1). Lake Forest, IL: Lake Forest College.

Hedrick, P., & Loeschcke, V. (1996). MHC and mate selection in humans? Trends in Ecology & Evolution, 11(1), 24.

Hummel, T., Rothbauer, C., Barz, S., Grosser, K., Pauli, E., & Kobald, G. (1998). Olfactory function in acute rhinitis. Annals of the New York Academy of Sciences, 855, 616-624.

Jacob, S., McClintock, M. K., Zelano, B., & Ober, C. (2002). Paternally inherited HLA alleles are associated with women's choice of male odor. Nature Genetics, 30, 175-179.

Klein, J. (1986). Natural history of the histocompatibility complex. New York, NY: Wiley.

Mercier, S. A. (2016). Potential effects of geography on MHC-disassortative mate selection in humans. In A. W. Shingleton (Ed.), NEUR482: Senior Seminar: Sex and Evolution (Vol. 1). Lake Forest, IL: Lake Forest College.

Milinski, M., Croy, I., Hummel, T., & Boehm, T. (2013). Major histocompatibility complex peptide ligands as olfactory cues in human body odour assessment. Proc. R. Soc. B, 280: 20122889. doi: 10.1098/rspb.2012.2889

Milinski, M., Griffiths, S., Wegner, K. M., Reusch, T. B. H., Haas-Assenbaum, A., & Boehm, T. (2005). Mate choice decisions of stickleback females predictably modified by MHC peptide ligands. PNAS, 102(12), 4414-4418.

Milinski, M., & Wedekind, C. (2001). Evidence for MHC-correlated perfume preferences in humans. Behavior Ecology, 12(2), 140-149.

Mostafa, T., El Khouly, G., & Hassan, A. (2012). Pheromones in sex and reproduction: Do they have a role in humans? Journal of Advanced Research, 3(1), 1-9.

Murphy, E. R., Brent, B. K., Benton, M., Pruitt, P., Diwadkar, V., Rajarethinam, R. P., & Keshaven, M. S. (2010) Differential processing of metacognitive evaluation and the neural circuitry of the self and others in schizophrenia: A pilot study. Schizophrenia Research, 116, 252-258.

Ober, C., Elias, S., Kostyu, D. D., & Hauck, W. W. (1992). Decreased fecundability in Hutterite couples sharing HLA-DR. American Journal of Human Genetics, 50, 6-14.

Penn, D. J., & Potts, W. K. (1999). The evolution of mating preferences and major histocompatibility complex genes. The American Naturalist, 153(2), 145-164.

Piertney, S. B., & Oliver, M. K. (2006). The evolutionary ecology of the major histocompatibility complex. Heredity, 96, 7-21.

Reznikoff-Etievant, M. F., Bonneau, J. C., Alaclay, D., Cavelier, B., Toure, C., Lobet, R., & Netter, A. (1991). HLA antigen-sharing in couples with repeated spontaneous abortions and the birthweight of babies in successful pregnancies. American Journal of Reproductive Immunology, 25, 25-27.

Richardson, D. S., Komdeur, J., Burke, T., & von Schantz, T. (2005). MHC-based patterns of social and extra-pair mate choice in the Seychelles warbler. Proc. R. Soc. B, 272, 759-767.

Roberts, S. C., Gosling, L. M., Carter, V., & Petrie, M. (2008). MHC-correlated odour preferences in humans and the use of oral contraceptives. Proc. R. Soc. B, 275, 2715-2722.

Santos, P. S. C., Schinemann, J. A., Gabardo, J., & Bicalho, M. G. (2005). New evidence that the MHC influences odor perception in humans: a study with 58 Southern Brazilian students. Hormones and Behavior, 47(4), 384-388.

Schwensow, N., Eberle, M., & Sommer, S. (2008). Compatibility counts: MHC-associated mate choice in a wild promiscuous primate. Proc. R. Soc. Lond. B, 275(1634). doi: 10.1098/rspb.2007.1433

Slade, R. W., & McCallum, H. I. (1992). Overdominant vs. frequency-dependent selection at MHC loci. Genetics, 132, 861-862.

Smith, K., Alberts, S. C., & Altmann, J. (2003) Wild female baboons bias their social behavior towards paternal half-sisters. Proc. R. Soc. Lond. B, 270, 503-510.

Thornhill, R., Gangestad, S. W., Miller, R., Scheyd, G., McCollough, J. K., & Franklin, M. (2003). Major histocompatibility complex genes, symmetry, and body scent attractiveness in men and women, Behavioral Ecology, 14(5), 668-678.

Trowsdale, J., & Knight, J. C. (2013). Major histocompatibility complex genomics and human disease. Annual Reviews: Genomics and Human Genetics, 14, 301-323.

Weckstein, L. N., Patrizio, P., Balmaceda, J. P., Asch, R. H., & Branch, D. W. (1991). Human leukocyte antigen compatibility and failure to achieve a viable pregnancy with assisted reproductive technology. Acta Eur. Fertil., 22, 103-107.

Wedekind, C., & Füri, S. (1997). Body odour preferences in men and women: do they aim for specific MHC combinations or simply heterozygosity? Proc. R. Soc. Lond. B, 264, 1471-1479.

Wedekind, C., & Seebeck, T. (1996). MHC and mate selection in humans? Trends in Ecology & Evolution, 11(1), 24-25.

Wedekind, C., Seebeck, T., Bettens, F., & Paepke, A. J. (1995). MHC-dependent mate preferences in humans. Proc. R. Soc. Lond. B, 260, 245-249.

Winternitz, J. C., Minchey, S. G., Garamszegi, L. Z., Huang, S., Stephens, P. R., & Altizer, S. (2013). Sexual selection explains more functional variation in the mammalian major histocompatibility complex than parasitism. Proc. R. Soc. Lond. B, 280(1769). doi: 10.1098/rspb.2013.1605

Wooldridge, L., Ekeruche-Makinde, J., van der Berg, H. A., Skowera, A., Miles, J. J., Tan, M. P., Dolton, G., Clement, M., Llewellyn-Lacey, S., Price, D. A., Peakman, M., & Sewell, A. K. (2012). A single autoimmune T cell receptor recognizes more than a million different peptides. The Journal of Biological Chemistry, 287, 1168-1177.

Yamazaki, K., Beauchamp, G. K., Egorov, I. K., Bard, J., Thomas, L., & Boyse, E. A. (1983). Sensory distinction between H-2b and H-2bml mutant mice. PNAS, 80, 5685-5688.

Yamazaki, K., Boyse, E. A., Mike, V., Thaler, H. T., Mathieson, B. J., Abbott, J., Boyse, J., Zayas, Z. A., & Thomas, L. (1976). Control of mating preferences in mice by genes in the major histocompatibility complex. The Journal of Experimental Medicine, 144, 1324-1335.

Photography by Abdullah Basith