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MHC-dependent mate preferences in humans

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SUMMARY

One substantial benefit of sexual reproduction could be that it allows animals (including humans) to react rapidly to a continuously changing environmental selection pressure such as coevolving parasites. This counteraction would be most efficient if the females were able to provide their progeny with certain allele combinations for loci which may be crucial in the parasite-host arms race, for example the MHC (major histocompatibility complex). Here we show that the MHC influences both body odours and body odour preferences in humans, and that the women's preferences depend on their hormonal status. Female and male students were typed for their HLA-A, -B and -DR. Each male student wore a T-shirt for two consecutive nights. The next day, each female student was asked to rate the odours of six T-shirts. They scored male body odours as more pleasant when they differed from the men in their MHC than when they were more similar. This difference in odour assessment was reversed when the women rating the odours were taking oral contraceptives. Furthermore, the odours of MHC-dissimilar men remind the test women more often of their own actual or former mates than do the odours of MHC-similar men. This suggests that the MHC or linked genes influence human mate choice today.

1. INTRODUCTION

Products of the MHC (major histocompatibility complex) play an important role in immune recognition. They bind short self or foreign peptides and present them, on the cell surface, to T-lymphocytes (Klein 1986; Hedrick 1994).

Several studies have shown that the MHC also influences mate choice in mice (Yamazaki *et al.* 1976; Egid & Brown 1989; Potts *et al.* 1991; reviews in Boyse *et al.* 1987; Potts & Wakeland 1993). Basing their choice on odours (Yamazaki *et al.* 1979; Boyse *et al.* 1987; Egid & Brown 1989), mice seem to look for or try to avoid certain alleles according to their own genotype (they mostly prefer mates of dissimilar MHC phenotypes). This preference could have evolved either through a strong advantage of certain MHC combinations under selection by pathogens (Hamilton & Zuk 1982; Potts & Wakeland 1993; Hedrick 1994; Wedekind 1994*a*), or, because mice often live in very small populations, as a mechanism for inbreeding avoidance i.e. the MHC being a marker for the degree of relatedness (Uyenoyama 1988; Potts & Wakeland 1993; Brown & Eklund 1994; Potts *et al.* 1994).

Humans have cultural incest taboos, and probably other mechanisms, to avoid inbreeding efficiently (Spiro 1958; Wolf 1966, 1970; May 1979). Nevertheless, body odours are a potential cue used in human mate choice. Furthermore, human noses can distinguish between two congenic mouse strains differing only in their MHC (Gilbert *et al.* 1986) and likewise, mice seem to be able to recognize human MHC-types from urine odours (Ferstl *et al.* 1992). Therefore we tested experimentally whether human body odours, and female preferences for them, are MHC-dependent.

2. METHODS

We typed 49 female students (average age: 25.2 years, s.d. = 4.0) and 44 male students (average age: 24.7 years, s.d. = 2.6) for their HLA-A, -B and -DR. HLA class I antigens were typed by serology on HLA typing plates (Biotest, Dreieich, Germany). HLA-DR antigens were determined by oligotyping (Tiercy *et al.* 1990). For this purposes the HLA-DRB1 genes were amplified by the polymerase chain reaction. This was followed by sequence-specific hybridization with biotinylated oligonucleotides, detected in a chemilumescence assay (Bettens *et al.* 1991). This method allows discrimination between the following HLA-DR alleles: DR1, DR2, DR3, DR4, DR7, DRw8, DR9, DRw10, DRw11, DRw12, DRw13, DRw14. Three females and one male could not be typed for the DR-antigens. For our experiments, they were assumed to be dissimilar on DR to the respective test partner (see below).

Steroids administered by the pill physiologically simulate pregnancy. We considered, therefore, that the pill was a possible confounding factor in our experiment and asked each female subject whether she was using oral contraceptives.

All test persons were students at the University of Bern and had forenames and surnames that are common in the German speaking part of Switzerland. Males and females probably did not know eachother, as they were from different courses (women mainly from biology and psychology, men

mainly from chemistry, physics and geography) and were unlikely to meet each other during the study. The men were asked to wear a T-shirt (100% untreated cotton, distributor: Virya, Zürich (CH)) during a Sunday and Monday night, to keep the T-shirt in an open plastic bag in between, and to live as much as possible 'odour-neutral' during these two days. They were provided with perfume-free detergent to wash clothes and bedclothes, and perfume-free soap to use from Sunday morning onwards. They were also provided with a list of odour-producing foods and asked to avoid them as well as any activities that could produce disturbing smells (for example, staying in smelly rooms, sexual activity, etc). They were advised not to use any deodorants, perfumes etc., to refrain from smoking tobacco or drinking alcohol, and to sleep alone in their bed.

On the following Tuesday test women were asked to rate the odours of six T-shirts each, three of them worn by men who were dissimilar to the rating woman's MHC (average number of dissimilar HLA-antigens = 5.9, s.d. = 0.26), and three worn by men who were more similar to it (average number of dissimilar HLA-antigens = 2.7, s.d. = 0.74). We tried to present every T-shirt as often to MHC-dissimilar women as to MHC-similar women (average difference of presentations to the two groups: −0.02, s.d. = 0.73). The presentation was random in every other respect, and the women did not know the degree of MHC-similarity of the men who had worn the T-shirts. The T-shirts were provided in numbered, glazed cardboard boxes laid out with plastic foil (PVDC), a triangular hole allowed the women to sniff the contents. Alone in a room, every woman scored the odours of the T-shirts for intensity (range 0–10) and for pleasantness and sexiness (range 0–10, 5 = neutral). A marked box with an unworn T-shirt was provided to allow the women to control for the T-shirt's own odour. The women were tested whenever possible in the second week after the beginning of menstruation (with pill: 11.4 d, s.d. = 4.3, without pill: 12.4 d, s.d. = 4.3, $t = -0.80$, $p_2 < 0.40$, two-tailed), as women appear to be most odour-sensitive at this time (Doty *et al.* 1981). We also asked them to prepare themselves for the experiment by taking care of their sense of smell. Therefore, the women had been asked to use a nose spray during 14 days before the experiment to support regeneration of the nasal mucous membrane if necessary (and also as a prophylactic against colds or 'flu), and each was given a copy of P. Süskind's novel 'Das Parfum' (Diogenes-Verlag) to sensitize their smell perception.

Each female subject scored the odours of six male subjects which resulted in 294 combinations of individual women sniffing on individual men's odours. Additionally each male odour was scored by two or more females (one of similar and one of dissimilar MHC-type). For the analyses shown in figures 1–3 we used the average scorings per male odour or per scoring female.

The data analyses were done with SYSTAT (version for Macintosh-computer).

3. RESULTS

The scores for sexiness are not shown in the figures as they were highly correlated with pleasantness (all scorings: $r = 0.85$, $n = 294$; for women who do not take the pill: $r = 0.87$, $n = 186$; for women who take the pill: $r = 0.83$, $n = 108$, p always $\ll 0.001$).

The pleasantness of men's body odours scored by different women depends on their respective MHC. Women who are not taking oral contraceptives and who are dissimilar to a particular male's MHC perceive his odour as more pleasant than do women whose

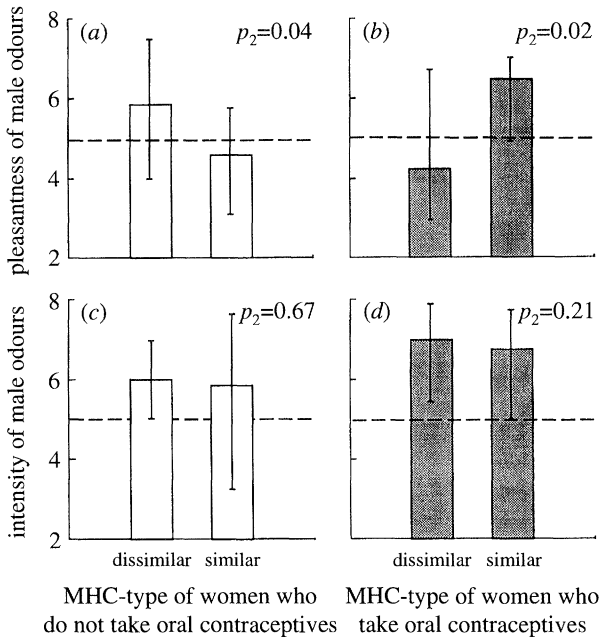

Figure 1. Average score per male (taking each male's odour as a statistical unit) by females who are similar or dissimilar on their MHC (medians and quartiles). (*a*) + (*c*) The odours were judged by females who did not take oral contraceptives (number of males = 38), and (*b*) + (*d*) judged by females who take the pill (number of males = 23). All *p*-values are two-tailed (Wilcoxon signed rank tests).

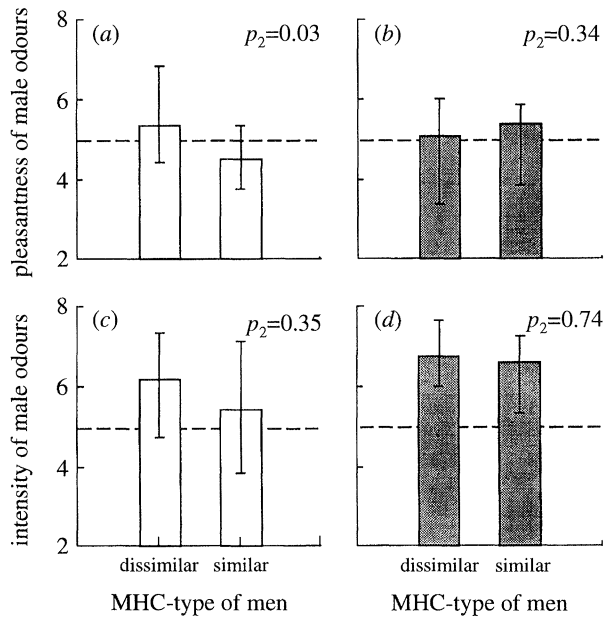

Figure 2. Average score per female of the body odours of males being similar or dissimilar on the MHC to the scoring females (medians and quartiles). (*a*) + (*c*) Females who do not take the contraceptive pill ($n = 31$), and (*b*) + (*d*) females who take the pill ($n = 18$). *P*-values are two-tailed (Wilcoxon signed rank tests).

MHC is more similar to that of the test man (see figure 1*a*). This difference in the scoring of odour pleasantness was reversed when the judging women were taking oral contraceptives. In this case, a man's body odour was scored as being more pleasant by women who are more similar on the MHC (see figure 1*b*).

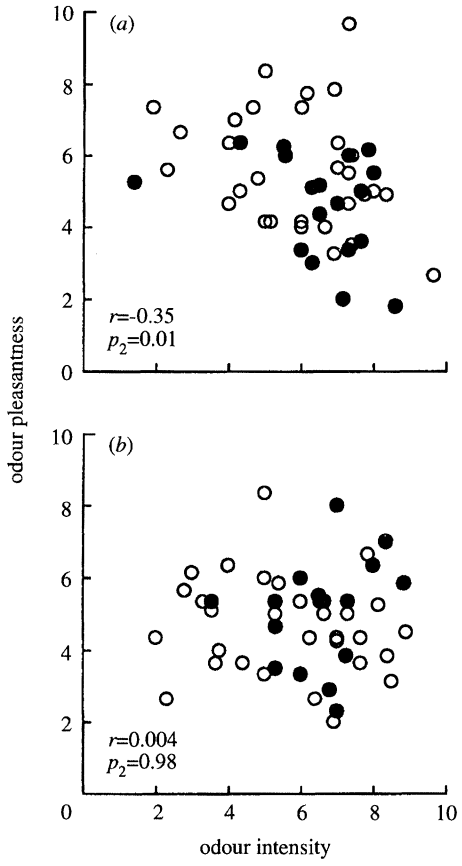

Figure 3. Relations between scores of odour pleasantness and odour intensity (all females pooled, $n = 49$ each). Average scorings per female of the body odours of three males each (*a*) being dissimilar on the MHC, and (*b*) being similar on it to the scoring female. The correlations do not differ significantly between females who take the contraceptive pill (●) and females who do not take the pill (○) (comparison between independent correlation coefficients (*a*) $Z = -0.13$, $p = 0.90$, (*b*) $Z = 1.28$, $p = 0.20$; all p-values are two-tailed).

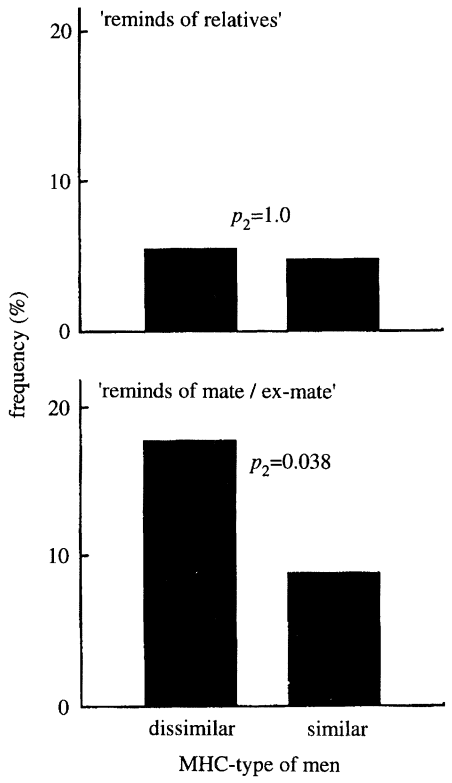

Figure 4. Frequency of women's memory associations by sniffing the odours of MHC-dissimilar men and of MHC-similar men with relatives, and with current or previous mates, respectively (Fisher exact tests, two-tailed). Most of the memory associations in the lower graph were by women who stated that they were sure they had not taken the contraceptive pill when they chose the particular mate they were remembered during the experiment (31 of total 39 cases, $Z = 3.68$, $p < 0.01$).

By taking each man as a statistical unit (see figure 1), we control for odour differences which are not MHC-dependent. The data are replotted in figure 2 using each woman as a statistical unit. Despite a certain loss of statistical power in this kind of analysis, we still observe analogous trends although not significant in the case of women taking the contraceptive pill (see figure 2*b*).

The female evaluations of odour intensities did not differ significantly between MHC-similar and dissimilar men in any comparison (see figure 1*c*,*d* and figure 2*c*,*d*). However, the relation between odour intensity and its pleasantness differed in the two groups: more intensive odours tend to be more unpleasant for women when they scored odours of MHC-dissimilar men (see figure 3*a*), whereas intensity and pleasantness did not correlate for women when they scored MHC-similar male odours (see figure 3*b*). This difference could indicate some properties of the physiology of odour perception which seem to be independent of steroids administered by the pill (see legend of figure 3).

Odours of MHC-dissimilar men reminded the female test persons of their own mates or ex-mates twice as often as those of MHC-similar men (see figure 4). This indicates that MHC-dependent body odour preferences play a role in actual mate choice.

4. DISCUSSION

The contraceptive pill seems to have a strong influence on odour preference. This indicates that steroids which are naturally released during pregnancy could change body odour preferences, leading to a preference for odours which are similar to those of relatives. This preference is probably not related to mate choice but may be comparable, to a certain degree, to the observation that female mice prefer MHC-similar individuals for communal nesting (Manning *et al.* 1992). Therefore, the contraceptive pill seems to interfere with natural mate choice. If the pill changes preferences for familiar as well as unfamiliar body odours then starting with the pill could have an influence on the stability of an already existing pair bond by influencing odour preference.

There is an increasing amount of work which indicates that the MHC may not only influence mate choice but also maternal selection thereafter. Couples who had not achieved a recognizable pregnancy after two or more attempts of in vitro fertilization (IVF) or tubal embryo transfer (TET) shared a significantly greater number of HLA antigens than did control couples who achieved a viable pregnancy with their first IVF or TET

cycle (Weckstein *et al.* 1991). Moreover, data on the North-American Hutterite population, a population isolate that proscribes contraception, suggest that longer intervals between successive births are associated with increased HLA sharing, and that this difference may result from losses occuring early in gestation, before the women would recognize pregnancy (Ober *et al.* 1988). However, MHC-associated selection may not only take place at this very early stage of pregnancy. Couples who suffer from recurrent spontaneous abortions often share a higher proportion of their MHC than control couples in many different populations (Beer *et al.* 1985; Bolis *et al.* 1985; Thomas *et al.* 1985; Karl *et al.* 1989; Ho *et al.* 1990; Koyama *et al.* 1991; Laitinen 1993). Also, newborn babies of such couples often have a reduced birth mass (Reznikoff-Etievant *et al.* 1991). In inbred populations, these effects could be adaptive, avoiding inbred offspring by using the MHC as a marker for kinship (Verrell & McCabe 1990). However, MHC-correlated abortions seem to be more widespread than would be expected from the frequency of highly inbred populations alone (May 1979). Instead, they could result from strategic 'decisions' of the woman's physiology about her investment in her baby, taking into account the anticipated selection (for example, by pathogens) on the offspring after birth (Wedekind 1994*b*). Of course, such a 'decision' is most probably no more conscious than, for example, the 'decision' to reject an allograft. Consistent with this may be the finding that spontaneous abortions in mice can be experimentally induced by the odour of a male which genetically differs only in his MHC from the fathering male (Yamazaki *et al.* 1983).

Among primates, humans seem to be most richly endowed with scent-producing glands (Stoddart 1991), and many examples illustrate strong links between the nose and human physiology and emotions (Stoddart 1991). Our findings show that some genetically determined odour components can be important in mate choice. The observed mate preference could be a means to efficiently react to pathogen pressures. If so, the negative consequences of disturbing this mechanism, by the use of perfumes and deodorants or by the use of the contraceptive pill during mate choice, need to be known by users.

All participants were informed about the aims of this study and gave their consent after the theoretical background and possible consequences of the study had been explained. We thank them for their interest and cooperation. Thanks also to Elisabeth Frei, Sandra Füri, Katrin Viragh, Barbara Streb and Martin Perlen for technical assistance, and to Manfred Milinski, Laurent Keller, Rudolf Sieg, Giorgina Bernasconi, Markus Frischknecht, Werner Pichler, William D. Hamilton, Jan Klein and the referees for discussion and comments on the manuscript. The project was supported by the Roche Research Foundation and the Swiss National Science Foundation (grant to M.M.).

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