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Review

How Does the Major Histocompatibility Complex Influence Behavior?

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Abstract. The major histocompatibility complex (MHC) encodes highly polymorphic cell surface glycoproteins that form the basis of immunological individuality. It has been postulated that MHC besides its role in immune defence also determines behavior through formation of specific odor cues. In addition several studies have implicated MHC disassortative odor and mating preferences in mice, rats, and humans. Further leading studies have suggested that mice and humans prefer to mate with MHC dissimilar individuals. Although the latter remains controversial, MHC dependent mating preferences provide a potentially important selective factor driving the polymorphisms of the MHC genes. Here we review some of the available data and hypotheses on the influence of the MHC on behavior and discuss its molecular and chemical basis.

Key words: major histocompatibility complex; human leukocyte antigen; odor; individual chemosignals; perception; mate choice.

Traditionaly the major histocompatibility complex (MHC) is well known for its regulatory function of the immune system. The classical class I antigens of the MHC are cell-surface glycoproteins expressed on nearly all viable cells in vertebrates. Originally the proteins encoded by the MHC were first described as transplantation antigens. The MHC comprises a group of genes located on the short arm of chromosome 6 in humans. Their protein products are called human leukocyte antigens (HLA). MHC class I and class II are polymorphic within any given population. The immunological explanation for MHC polymorphism is based on its protective function against lethal pathogens that would otherwise extinguish a species by epidemic infection. However, the high degree of heterozygosity found in natural populations of most species seems to be promoted by non-disease-based selection such as mating preferences and selective block of pregnancy.

In the seventies a novel role of the MHC was described. Polymorphic genes of the MHC were shown to determine, in part, the chemosensory identity or odortype of individuals. KALMUS[17] was the first who observed that dogs had difficulty in distinguishing odors of identical twins. Further, THOMAS[31] speculated that the MHC might play a role in social behavior as an expression of genetic individuality, but was not able to explain how and why it may be involved.

Olfaction, Kin Recognition and Behavior

Early studies into the external expression of the MHC demonstrated that olfactory cues associated with the MHC selectively influence mate choice and the frequency of pregnancy blocks in inbred strains as well as in seminatural populations of mice[1, 24, 34]. In addition to these experiments, different studies revealed that the MHC is associated with the expression of olfactory cues in rats and humans[4]. Further, urine was found to

be a potent source of distinctive odors, determined by hematopoetic cells. All these studies support evidence that MHC-determined mate preferences are mediated by urinary chemosignals[9-11, 33]. BROWN et al.[5] could also demonstrate that urines from MHC-congenetic rats are discriminable in behavioral studies.

The advantage of MHC-different mate preference is based on the avoidance of inbreeding which leads to maintainance of an extraordinary genetic diversity. It is expected that MHC heterozygous offsprings are more resistant to infectious diseases than homozygous individuals of the same species[16], and seem to be more protected against the process of natural selection. A possible second influence of the MHC on reproduction is the well known pregnancy-block effect (Bruce effect)[6]. Both of these influences rely on chemosensory imprinting.

Body Odor, Perception and Mate Choice in Humans

Most studies on the influence of the MHC on chemosignals have been performed in rodents and evidence from these studies suggests that mate selection is influenced by MHC haplotypes, with preferences for dissimilar partners. Recently, it has been speculated[2, 3] that a similar phenomenon may occur in humans. PORTER and MOORE[23] as well as LORD and KASPRZAK[20] reported that individual specific body odors do indeed play a role in human self-perception and recognition of offspring. The MHC antigens are known as HLA (human leukocyte antigens) in humans. FERSTL et al.[13] studied peculiar odor perception phenomena in humans. They have demonstrated that 55% of individuals identified by strong body odor are HLA-A23, -A24 and/or HLA-B62, -B63 positive with a frequency much higher than that in a normal population. Along these lines, ZAVAZAVA et al.[35] measured high serum concentrations of soluble class I HLA-molecules of HLA in HLA-A23, -A24 and -B62 individuals. This result supports the idea that high soluble HLA levels, which were also detected in sweat, are precursors for individual specific odorants and could perhaps explain the odor intensity of HLA--A23, -24 and HLA-B62 persons. These findings indicate involvement of HLA on body odor.

In a more recent study WEDEKIND et al.[32] reported on a so called "T-shirt-test". Women were asked to qualify the odor of T-shirts worn by subjects with HLA-types similar or dissimilar to that of their own. The T-shirt-odors from subjects with a dissimilar HLA--specifities were percieved to be pleasant; the body odors derived from subjects with similar HLA-types were identified as unpleasant. Interestingly, a different or weaker effect in odor preference was found if the tested women were under oral contraceptives. The body odors from HLA similar individuals were characterized as pleasant or attractive and that of persons with dissimilar HLA-alleles as neutral or unpleasant. These studies may indicate that odor preferences in humans may be linked to the HLA and are obviously influenced by hormonal influences. More precise investigations were performed by OBER et al.[21] who determined whether HLA-based mate choice might be detectable in Hutterites, an inbred, ethnically homogenous population with a limited repertoire of HLA genes. Four hundred and eleven Hutterite couples were tissue-typed and the number of couples expected to match for a haplotype was calculated. Their data revealed fewer matches for HLA haplotypes between spouses than expected. In summary, their results were consistent with the conclusion that Hutterite mate choice is influenced by HLA, with an avoidance of spouses with identical haplotypes. In addition, KRAUL et al.[18] monitored electropysiological brain responses in humans to different body odors. The brain responses to HLA-similar odor donors were found to be larger and faster than brain responses to HLA-dissimilar donors and HLA-similar donors were subjectively judged as less attractive.

Hypotheses to the Expression of MHC Associated Odor Signals

Several models have been put forward to explain odor formation and the role of genetic differences in imparting individual-specific odors. Soluble MHC class I molecules are present in blood, serum, sweat and urine[15, 25]. It was speculated that these molecules modulate body odor. Although their molecular size is such that they themselves cannot escape into the gas form, their degradation products might constitute individuality.

Indeed class I molecules are extensively degraded in urine[29]. It was therefore suggested that aromatic amino acids, characteristic of the variable sequences in the heavy chain, contribute the aromatic signals. This explanation was, however, not satisfactory since most purified amino acids do not smell. PEARSE-PRATT et al.[22] hypothesised that volatiles produced by the commensal flora are bound by soluble MHC molecules, which release them on exposure to the environment. In agreement with this explanation foreign purified MHC molecules injected into the circulation of rats changed their urine odor to that of the foreign strains.

CROZIER[7] postulated that the immuno-regulatory function of the class I defines variations in the commensal bacterial flora which generates individual urine odors. This indirect association between class I phenotype and urine odor was not convincing, because it could not be shown that the commensal phenotype of an individual is stable with time.

A complementary hypothesis by ROSER et al.[26] was suggested in which the commensal flora acts as the source of multiple volatile aromatics while the class I molecule acts as an individual-specific carrier. This carrier selects and binds a unique cocktail of the bacterial volatiles and transports and releases them in the urine. Similarly, SINGH et al.[30] and ROSER et al.[26] have demonstrated that germ free and specific pathogen-free rats do not excrete individual odors in their urine, suggesting a role of commensal flora. However, these findings could not be confirmed in mice.

Some groups[12, 14] have focusted on the existence of olfactory receptors which may be associated with the MHC. LANCET and BEN-ARIE[19] have described high sequence homology between the olfactory receptor-gene family and regions of the MHC class I. These studies are indeed exciting, however, direct influence on the involvement of these receptors is still missing.

Chemical Signals

Although behavioral studies have provided evidence that the MHC does indeed influence body odor, the nature of the chemical signals has remained puzzling. SCHWENDE et al.[27] examined H-2 associated odors in inbred strains of mice and found a correlation between the genetic relatedness with regard to the MHC and the similarity of chromatograms of urine odors obtained by capillary gas chromatography. Their results indicated that a pattern of secondary metabolites rather than the presence of specific components in the urine may serve as odorant cues specific to the MHC type.

SINGER et al.[28] identified characteristic quantitative differences in the urine odors of H-2 congenetic strains using gas chromatography and suggested that carboxylic acids are probable carriers of odorants. In a study by EGGERT et al.[8] specific olfactory cues of urine samples from genetically defined inbred mice were analyzed by gas chromatography. In contrast to SINGER et al.[28] and SCHWENDE et al.[27], they presented data which provide evidence of a small number of specific components associated with the MHC type but there is no information available on the chemical nature of these compounds.

Final Remarks

In summary, behavioral studies are unequivocal about the involvement of the MHC in imparting individuality. However, several problems still require to be solved. Firstly, it is still unclear whether the classical MHC molecules themselves are directly linked to individual body odor or not. Their association with particular behavioral patterns may be interpreted as guilt by association unless direct evidence is brought up. Some other genes within the MHC may equally participate in determining individuality. Secondly, it still remains unresolved whether the individual-specific odor cues are MHC-derived or not. Thirdly, the role of commensal flora is still not known. However, undoubtely the break-down of the MHC products and MHC-associated proteins is likely to be important. Finally, the olfactory receptor genes and pseudo-genes identified within the MHC require further studies to verify their function and possible link to olfactory individuality.

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