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Individual Differences and the Chemical Senses

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Introduction

A powerful approach in the search for general principles in biology focuses on analyses of differences among individuals and groups. Such differences arise from variation in genes, variation in individual experiences and their interactions. The chemical senses provide a particularly rich source of such differences in both signal perception and signal production. In the following essay, we describe how studies focusing on variation in the production of odorous compounds illuminate important aspects of how animals communicate with body odors.

By gazing at a person's face, a remarkable amount of information can be obtained. More or less constant characteristics that can often be identified include ethnicity, gender, age and individual identity. More effervescent information, such as mood, motivational state and even health status, may also be inferred. Visual signals may not always be interpreted correctly—eyewitnesses to crimes may mistake one individual for another—or the message itself may be falsified, for example by an actor. Yet it is remarkable how accurate people are at making these distinctions and how difficult it is to explain what exactly distinguishes one person from another or how one knows that someone is angry or sick. For many animals vision is less important than olfaction in making these discriminations; indeed, the precision by which animals can identify characteristics of each other by scent is almost beyond understanding. Nevertheless, it is this area we have been investigating for many years.

Odorous signals of individuality

We have focused on the role of the genes in the major histocompatibility complex (MHC) in provisioning mice with an odor we have termed its MHC odortype. These odors are involved in mate choice, parent–infant interactions and perhaps other aspects of the mouse's social and reproductive behavior. This work has been extensively reviewed elsewhere and will not be detailed here [see Table 1, modified from Beauchamp and Yamazaki (2003), which provides references for much of the evidence for mice, rats and humans]. These many studies leave no doubt that MHC genes code for volatile (and perhaps a non-volatile) signals in body fluids that serve communicatory functions.

The identity of the volatile signals remains to be fully determined. We previously reported (Singer *et al.*, 1997) that the acidic fraction of urine contains a series of compounds that differ in amounts in mice with differing MHC types. Recently we have identified several dozen components in urine of MHC congenic mice that differ according to MHC type (Willse *et al.*, submitted for publication) and we find, consistent with our previous work, that all differences are quantitative rather than qualitative. That is, mice apparently differ in the pattern of volatiles rather than in the presence or absence of particular urinary odorants.

Although there are several related hypotheses to explain how these genes code for odortypes (Pearse-Pratt *et al.*, 1992), the pathway from gene to odor is still not understood. MHC genes code for proteins that bind intracellular peptides and display them on the cell surface for immune surveillance. The odorants could be breakdown products of the MHC proteins, breakdown products of the bound peptides, or have some other source (e.g. produced by MHC-regulated bacterial differences among mice). That these odorants are found, albeit at low levels, in serum after it has been treated with proteases suggests that they are ubiquitous.

MHC odortypes are clearly not the only signals of olfactory individuality. MHC differences in urine volatiles account for roughly one half of the individual variance. Genes on the X and Y chromosomes are also involved. Recent evidence implicates mouse urinary proteins as signals of individual identity (Hurst *et al.*, 2001). This multiplicity is not surprising. If one considers the human visual analogy, it would be naive to assume that a single sensory attribute or feature would account for something as complex and patterned as individual recognition. However, we hypothesize that MHC odortypes, due to the inherent extensive genotypic variability of this set of genes, may be primary much like facial recognition seems primary for human individual identity.

That dogs are apparently able to identify and follow individual people suggests that each person, like each mouse, also has a unique odor, as was reported many years ago by the deaf–blind writer Helen Keller (Keller, 2003). As shown in Table 1, there are a number of reports linking human olfactory differences to differences in the MHC. None of these is definitive, however. Studies underway in our laboratories, as well as in the laboratories of several other investigators, should provide new insights into this question in the not-to-distant future.

Odorous signals of infection

As referenced in Table 1, a mouse's odortype is evident as early as 1 day post-partum. This led us to hypothesize that the odortype of a fetus might also be expressed in the pregnant female mouse odortype as indeed turned out to be the case. Presumably, the MCH-determined volatiles of fetal origin mix with those of the mother-to-be to form a combined odortype. If one views the fetus as a kind of 'infection', then this raises the issue of whether other kinds of infection might also be identified by changes in body odor.

This idea has a long history in medicine but rigorous examination with an animal model has been rare. A number of studies indicate that an animal's odors change following illness by induced infectious agents (Penn and Potts, 1998a), but little is known about the mechanisms of these odor changes or how ubiquitous disease-related odor changes are. For example, if an animal's odor changed following infection in a non-specific manner, due to changes in eating patterns or to stress, this would not be particularly interesting as the change would not specifically reflect the infection. More interesting would be if the change was a more fundamental specific response to a particular disease vector. In the latter case, it might be possible to diagnose disease might be determinable based on only the odor.

To investigate this issue, we turned to an animal model for which genetic and environmental factors are held constant and only the presence or absence of the disease vector is allowed to vary. The model system is the mouse mammary tumor virus (MMTV) (Luther and Acha-Orbea, 1997). Mammary tumors caused by this virus are notably lacking in cachectic, metastatic and other general systemic

Table 1 MHC (major histocompatibility complex) genes and body odor

Evidence that the MHC genes regulate individual odortypes in mice (M), rats (R) and humans (H)	References
Suggestive evidence	
MHC mating preferences (M, H)	Mouse: Yamazaki *et al.*, 1976, 1978, 1988; Egid and Brown, 1989; Eklund *et al.*, 1991; Potts *et al.*, 1991 Human: Wedekind *et al.*, 1995; Ober *et al.*, 1997
Female–female association (M)	Mouse: Manning *et al.*, 1992
Pup retrieval (M)	Mouse: Yamazaki *et al.*, 2000
Neuroendocrine consequences (M, H)	Mouse: Yamazaki *et al.*, 1983b; Human: Ober *et al.*, 1988
Neural activity pattern in the central neural (M)	Mouse: Schaefer *et al.*, 2001, 2002
Direct evidence: choice experiments	
Male attraction to pregnant females (M)	Mouse: Beauchamp *et al.*, 2000
Pup attraction to familial odors (M)	Mouse: Yamazaki *et al.*, 2000
Soiled shirt odor preferences (H)	Human: Jacob *et al.*, 2002; Wedekind and Furi, 1997
Direct evidence: learning experiments (Y maze and olfactometer)	
Congenic animals; adults, pups (M)	Mouse: Yamazaki *et al.*, 1979, 1982, 1992; Yamaguchi *et al.*, 1981; Beauchamp *et al.*, 1985, 1990
Germ-free animals (M)	Mouse: Yamazaki *et al.*, 1990
Chemical fractions—congenic animals (M)	Mouse: Singer *et al.*, 1997
MHC mutants (M)	Mouse: Yamazaki *et al.*, 1983a
Chimeric animals (M)	Mouse: Yamazaki *et al.*, 1985
Pregnant females according to fetal MHC type (M)	Mouse: Beauchamp *et al.*, 1994
Various body fluids (M)	Mouse: Yamazaki *et al.*, 1999
Out bred	Mouse: Yamazaki *et al.*, 1994
MHC deficient animals	Mouse: Bard *et al.*, 2000
Direct evidence: learning experiments (habituation)	
Congenic animals (M, R)	Mouse: Penn and Pots, 1998b; Rat: Brown *et al.*, 1987; Singh *et al.*, 1987, 1988
MHC mutants (M)	Mouse: Carroll *et al.*, 2001
Germ-free animals (R)	Rat: Singh *et al.*, 1990; Shellinck *et al.*, 1995

effects on the host that might be expected to alter body odor in a non-specific manner.

Infectious MMTV is acquired by newborn pups as they suckle on mothers that shed virus into milk (Luther and Acha-Orbea, 1997). MMTV replicates by reverse transcription of its RNA genome into DNA, leading to chromosomal integration in infected cells. Since infection is easily induced when the virus is received during the early postnatal period of immunological tolerance, and since MMTV can be transmitted in the milk, strains of genetically identical mice can be produced by foster nursing. These mice differ from non-exposed mice of the same inbred strain only in presence of productive MMTV infection. During the course of an MMTV infection, a virally encoded protein termed the superantigen (Sag) is presented by the MHC class II on B cells to T cells. After their activation, these T cells are deleted from the immune repertoire through apoptosis. Because MMTV infection has such a profound effect on the T cell repertoire of infected animals, it is possible that the viral phenotypic odor we have reported (see below) is related to this alteration in the immune system mechanisms.

MMTV can also be transmitted genetically as an endogenous provirus. Most mouse strains have one or more endogenous proviruses but they rarely produce viral particles that can be transmitted exogenously. Nevertheless, as with exogenous MMTV, endogenous proviruses cause specific deletion of T cell subpopulations during the neonatal shaping of the immune repertoire. Consequently, MMTV transgenic mice, rather than showing a gradual deletion of T cells, are essentially deleted from birth. If the effects of exogenous MMTV are due to activity of the viral genes, endogenous MMTV should also be characterized by a specific odor.

Our MMTV studies also used our standard associative learning Y-Maze training and testing procedures. Methods and results are described in detail Yamazaki *et al.* (2002). Very briefly, mice were successfully trained to discriminate between urine odors of mice that were identical except for the absence or presence of MMTV infection

transmitted either environmentally, from mother to offspring, or genetically. This odor distinction based on the presence of virus occurs in the absence of overt disease; all urine donor animals appeared healthy and there was no influence of infection on body weight.

The mechanism by which this occurs is not known. After ingestion of infected milk, MMTV crosses the intestinal barrier of neonates and invades the lymphoid cells and spreads to all lymphoid organs before arriving at the epithelial cells of the mammary glands, its jumping-off point to the next generation. Because there is a superantigen encoded in the virus, infection is accompanied by deletions in the T cell repertoire; this also occurs in genetically transmitted MMTV. Thus the odor differences observed between mice with and without MMTV may be attributable to MMTV-associated perturbations of the immune system rather than to the virus itself.

A number of studies (Penn and Potts, 1998a,b) have demonstrated that body odors of animals infected with certain parasites (e.g. protozoa, nematodes) and viruses are avoided. Generally, these studies have evaluated odors of animals with acute illness. It would be of interest to determine whether mice harboring latent exogenously transmitted MMTV infection are also avoided. There are indications that endogenous MMTV provides protection against exogenous infection. Consequently, a mating preference for mice with genetically based MMTV might be expected.

Whether these odors are specific to different types of MMTV or to other viruses, and the extent to which viral and other diseases can be diagnosed prior to any overt symptoms in mice or other organisms such as humans, should be investigated. There have been reports of dogs' abilities to detect skin cancers (Pickel *et al.*, 2004). Our current model system is particularly timely since several recent studies (e.g. Stewart, 2002) have implicated MMTV-like genes in some human breast cancers. Also, there is a wide variety of other viral diseases, for which obvious symptoms are slow to develop, that could be investigated for unique odor production.

Summary

In many species, body scent can convey much information between individuals. Information on individual identity, prominent in mouse body odors and particularly dependent on MHC genes, has been strongly implicated in mate choice, familial care and neuroendocrine balance. Information on health status, also definitively demonstrated in mice, may play an important role in social behavior although studies to verify this need to be conducted. Further studies in humans of both individual olfactory identity and odors associated with disease may lead to various practical outcomes and could provide important justification for increased study of odor, olfaction and olfactory communication.

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References

Bard, J., Yamazaki, K., Curran, M., Boyse, E.A. and **Beauchamp, G.K.** (2000) *Effect of β_2m gene disruption on MHC-determined odortypes*. Immunogenetics, 51, 514–518.

Beauchamp, G.K. and **Yamazaki, K.** (2003) *Chemical signalling in mice.* Biochem. Soc. Trans., 31, 147–151.

Beauchamp, G.K., Yamazaki, K., Wysocki, C.J., Slotnick, B.M., Thomas, L. and **Boyse, E.A.** (1985) *Chemosensory recognition of mouse major histocompatibility types by another species*. Proc. Natl Acad. Sci. USA, 82, 4186–4188.

Beauchamp, G.K., Yamazaki, K., Duncan, H., Bard, J. and **Boyse, E.A.** (1990) *Genetic determination of individual mouse odor*. In MacDonald, D.W. *et al.* (eds), Chemical Signals in Vertebrates 5. Oxford University Press, London, pp. 244–254.

Beauchamp, G.K., Yamazaki, K., Curran, M., Bard, J. and **Boyse, E.A.** (1994) *MHC-mediated fetal odortypes expressed by pregnant females influence male associative behaviour*. Immunogenetics, 39, 109–113.

Beauchamp, G.K., Curran, M. and **Yamazaki, K.** (2000) *MHC-mediated fetal odortypes expressed by pregnant females influence male associative behaviour*. Anim. Behav., 60, 289–295.

Brown, R.E., Singh, P.B. and **Roser, B.** (1987) *The Major Histocompatibility Complex and the chemosensory recognition of individuality in rats*. Physiol. Behav., 40, 65–73.

Carroll, L., Penn, D.J. and **Potts, W.K.** (2001) *Discrimination of MHC-derived odors by untrained mice is consistent with divergence in peptide-binding region residues*. Proc. Natl Acad. Sci. USA, 99, 2187–2192.

Egid, K. and **Brown, J.L.** (1989) *The Major Histocompatibility Complex and female mating preferences in mice.* Anim. Behav., 38, 548–549.

Eklund, A., Egid, K. and **Brown, J.L.** (1991) *The major histocompatibility complex and mating preferences of male mice.* Anim. Behav., 42, 693–694.

Hurst, J.L., Payne, C.E., Nevison, C.M., Marie, A.D., Humphries, R.E., Robertson, D.H.L., Cavaggioni, A. and **Beynon, R.J.** (2001) *Individual recognition in mice mediated by major urinary proteins*. Nature, 414, 631–634.

Jacob, S., McClintock, M.K., Zelano, B. and **Ober, C.** (2002) *Paternally inherited HLA alleles are associated with woman's choice of male odor*. Nat. Genet., 30, 175–179.

Keller, H. (2003) The world I live in. New York Review Books, New York.

Luther, S.A. and **Acha-Orbea, H.** (1997) *Mouse mammary tumor virus: immunological interplays between virus and host*. Adv. Immunol. 65, 139–243.

Manning, C.J., Wakeland, E.K. and **Potts, W.K.** (1992) *Communal nesting patterns in mice implicate MHC genes in kin recognition*. Nature 360, 581–583.

Ober, C., Elias, S., O'Brien, E., Kostyyu, D., Hauck, W.W. and **Bombard, A.** (1988) *HLA sharing and fertility in Hutterite couples: evidence for prenatal selection against compatible fetuses.* Am. J. Reprod. Immunol. Microbiol., 18, 111–115.

Ober, C., Weitkamp, L.R., Cox, N., Dytch, H., Kostyyu, D. and **Elias, S.** (1997) *HLA and mate choice in humans.* Am. J. Hum. Genet., 61, 497–504.

Pearse-Pratt, R., Schellinck, H., Brown, R. and **Roser, B.** (1992) *Evolutionary and immunological implications of the role of the MHC in olfactory signaling* In Doty, R.L. and Muller-Schwarze, D. (eds), Chemical Signals in Vertebrates 6. Plenum Press, New York, pp. 167–173.

Penn, D. and **Potts, W.K.** (1998a) *Chemical signals and parasite-mediated sexual selection.* Trends Ecol. Evol., 13, 391–396.

Penn, D. and **Potts, W.K.** (1998b) *Untrained mice discriminate MHC-determined odours*. Physiol. Behav., 63, 235–243.

Pickel, D., Manucy, G.P., Walker, D.B., Hall, S.B. and **Walker, J.C.** (2004) *Evidence for canine olfactory detection of melanoma*. Appl. Anim. Behav. Sci. (in press).

Potts, W.K., Manning, C.J. and **Wakeland, E.K.** (1991) *Mating patterns in seminatural populations of mice influenced by MHC genotype*. Nature, 352, 619–621.

Schaefer, M.L., Young, D.A. and **Restrepo, D.** (2001) *Olfactory fingerprints for major histocompatibility complex-determined body odors*. J. Neurosci., 21, 2481–2487.

Schaefer, M.L., Yamazaki, K., Osada, K., Restrepo, D. and **Beauchamp, G.K.** (2002) *Olfactory fingerprints for major histocompatibility complex-determined body odors. II. Relationship between odor maps,genetics, odor composition and behavior*. J. Neurosci., 22, 9513–9521.

Shellinck, H.M., Rooney, E. and **Brown, R.E.** (1995) *Odors of individuality of germ-free mice are not discriminated by rats in a habituation-dishabituation procedure.* Physiol. Behav., 57, 1005–1008.

Singer, A.G., Beauchamp, G.K. and **Yamazaki, K.** (1997) *Volatile signals of the Major histocompatibility complex in male mouse urine*. Proc. Natl Acad. Sci. USA, 94, 2210–2214.

Singh, P.B., Brown, R.E. and **Roser, B.** (1987) *MHC antigens in urine as olfactory recognition cuses.* Nature, 327, 161–164.

Singh, P.B., Brown, R.E. and **Roser, B.** (1988) *Class I transplantation antigens in solution in body fluids and in the urine: Individuality signals to the environment*. J. Exp. Med., 168, 195–211.

Singh, P.B., Herbert, J., Roser, B., Arnott, L., Tucker, D.K. and **Brown, R.E.** (1990) *Rearing rats in gern-free environment eliminates their odors of individuality*. J. Chem. Ecol., 16, 1667–1682.

Stewart, A.F.R. (2002) *Identification of human homologues of the mouse mammary tumor virus receptor.* Arch. Virol., 147, 577–581.

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

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

Yamaguchi, M., Yamazaki, K., Beauchamp, G.K., Bard, J., Thomas, L. and **Boyse, E.A.** (1981) *Distinctive urinary odors governed by the major histocompatibility locus of the mouse.* Proc. Natl Acad. Sci. USA, 78, 5817–5820.

Yamazaki, K., Boyse, E.A., Mike, V., Thaler, H.T., Mathieson, B.J., Abbott, J., Boyse, J., Zayas, Z.A. and **Thomas, L.** (1976) *Control of mating preferences in mice by genes in the Major Histocompatibility Complex*. J. Exp. Med., 144, 1324–1335.

Yamazaki, K., Yamaguchi, M., Andrews, P.W., Peake, B. and **Boyse, E.A.** (1978) *Mating preferences of F_2 segregants of crosses between MHC-congenic mouse strains.* Immunogenetics, 6, 253–259.

Yamazaki, K., Yamaguchi, M., Baranoski, L., Bard, J., Boyse, E.A. and **Thomas, L.** (1979) *Recognition among mice: evidence from the use of a Y-maze differentially scented by congenic mice of different major histocompatibility types*. J. Exp. Med., 150, 755–760.

Yamazaki, K., Beauchamp, G.K., Bard, J., Thomas, L. and **Boyse, E.A.** (1982) *Chemosensory recognition of phenotypes determined by the Tla and H-2K regions of chromosome 17 of the mouse*. Proc. Natl Acad. Sci. USA, 79, 7828–7831.

Yamazaki, K., Beauchamp, G.K., Egorov, I.K., Bard, J., Thomas, L. and **Boyse, E.A.** (1983a) *Sensory distinction between H-2^b and H-2^{bm1} mutant mice.* Proc. Natl Acad. Sci. USA, 80, 5685–5688.

Yamazaki, K., Beauchamp, G.K., Wysocki, C.J., Bard, J., Thomas and **L. Boyse, E.A.** (1983b) *Recognition of H-2 types in relation to the blocking of pregnancy in mice*. Science, 221, 186–188.

Yamazaki, K., Beauchamp, G.K., Thomas, L. and **Boyse, E.A.** (1985) *The hematopoietic system is a source of odorants that distinguish major histocompatibility types.* J. Exp. Med., 162, 1377–1380.

Yamazaki, K., Beauchamp, G.K., Kupniewski, D., Bard, J., Thomas, L. and **Boyse, E.A.** (1988) *Familial imprinting determines H-2 selective mating preferences*. Science, 240, 1331–1332.

Yamazaki, K., Beauchamp, G.K., Imai, Y., Bard, J., Phelan, S.P., Thomas, L. and **Boyse, E.A.** (1990) *Odortypes determined by the major histocompatibility complex in germ-free mice*. Proc. Natl Acad. Sci. USA, 87, 8413–8416.

Yamazaki, K. *et al.* (1992) *Expression of urinary H-2 odortypes by infant mice.* Proc. Natl Acad. Sci. USA, 89, 2756–2758.

Yamazaki, K., Beauchamp, G.K., Shen, F.W., Bard, J. and **Boyse, E.A.** (1994) *Discrimination of odortypes determined by the major histocompatibility complex among outbred mice*. Proc. Natl Acad. Sci. USA, 91, 3735–3738.

Yamazaki, K., Beauchamp, G.K., Singer, A., Bard, J. and **Boyse, E.A.** (1999) *Odortypes: Their origin and composition*. Proc. Natl Acad. Sci. USA, 96, 1522–1525.

Yamazaki, K., Beauchamp, G.K., Curran, M., Bard, J. and **Boyse, E.A.** (2000) *Parent-progeny recognition as a function of MHC odortype identity.* Proc. Natl Acad. Sci. USA, 97, 10500–10502.

Yamazaki, K., Boyse, E.A., Bard, J., Curran, M., Kim, D., Ross, S.R. and **Beauchamp, G.K.** (2002) *Presence of mouse mammary tumor virus specifically alters the body odor of mice*. Proc. Natl Acad. Sci USA, 99, 5612–5615.