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 evanescent 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-too-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...
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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.

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

<table>
<thead>
<tr>
<th>Evidence that the MHC genes regulate individual odortypes in mice (M), rats (R) and humans (H)</th>
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<td>Congenic animals (M, R)</td>
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<td>MHC mutants (M)</td>
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<td>Germ-free animals (R)</td>
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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 super-antigen 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 effects 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


