Mating types in yeast, vomeronasal organ in rodents, homosexuality in humans: Does a guiding thread exist?

by Daniele Oliva

Correspondence to: Dr. Daniele Oliva, Ph.D.
via Annibale 52
90149 Palermo, ITALY
TEL: +39 333 209 7533
E-MAIL: oliva12@libero.it

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Abstract Pheromones and their receptors are the molecules used by very different organisms in order to join two haploid cells. It happens evidently in yeast, since the two blending haploid cells are also the two mating organisms, whereas in rodents pheromone receptors are the triggers of the vomeronasal system which, supervising sexual behaviors, is responsible for copulation and therefore for fertilization. The debate is still open about the real significance of pheromones in humans but a working vomeronasal organ, able to recognize pheromones of the same sex, could be the simplest biological explanation of homosexuality. This hypothesis is discussed and connected with some well known experimental data.

Evolutionistic advantages of sexual reproduction are well known: the fusion of two haploid cells, arisen by meiosis, generating one diploid zygote, allows the creation of individuals with always different genomic inheritance, high genetic variability in the population and better possibilities of adaptation to the environment.

Indeed a simple unicellular organism, the yeast *Saccharomyces cerevisiae*, presents haploid cells of two different "mating types" (sexes), a and α [1]. Cells of different mating types are able to recognize each other, by production of specific polypeptide pheromones and their bond to superficial receptors, proteins belonging to the family of GPCRs (G protein-coupled receptors), provided with seven hydrophobic domains crossing the cellular membrane [2]: when receptors bound the pheromones produced from the opposite mating type, they induce a cascade of cellular reactions leading to the fusion of the two cells a and α and to the creation of a diploid organism [3]. In case of much more complicated organisms, as mammals, the fusion of two haploid cells, egg and sperm, bears the same result.

It looks that well functioning mechanisms are well preserved. In fact animals reproducing by internal fertilization have to recognize each other before mating and it is well demonstrated, at least in rodents, that sexual behaviors are controlled by the vomeronasal system [4,5]: through the accessory olfactory bulb, the medial preoptic area and the medial amygdala, some hypothalamic nuclei are connected to the vomeronasal organ, a sensory pit situated on both sides of the nasal septum and able to recognize pheromones produced by individuals of the opposite sex [6]. Both vomeronasal organ and system are sexually dimorphic [7]. What has that got to do with yeast? Also in rodents pheromone receptors are proteins with seven hydrophobic domains crossing the membrane of sensorial cells [8]. This time the immediate consequence of the bonding between pheromone and receptor is a single nervous impulse

toward the hypothalamus, but the final result will be always the same: the fusion of two haploid cells to form one diploid cell. Anyhow the trigger, releasing the whole chain of events ending with the fertilization, utilizes the same molecules already used in yeast: the pheromone receptors.

If probably most of us have no difficulty to see this guiding thread flowing trough all eucaryotic evolution, till rodents, it is not as simple when we are directly involved as human beings. Since 1991, with the discovery that the vomeronasal organ is present and working also in humans [9-12], a debate has arisen in the scientific community about the real role of pheromones in human sexual behaviors, but after more than a decade, there are not clear and final answers in the affirmative or negative: sometimes the vomeronasal organ is almost always present [11], sometimes this is not really true [13]; for some researchers it is working [12], but for others there is no connection to the higher nerve centers [14]. I never had the chance of studying experimentally the problem, but in my opinion it seems very difficult that a mechanism, so well preserved since the dawning of the sexual reproduction, was lost in the short lapse of time, and of genes, that separate us from rodents.

Yet it exists a simple way for having new information about the putative role of the vomeronasal organ in human sexual behavior, but I didn't find any notice about it, also in recent literature [15,16]: in 1991 the use of an apparatus was reported, able to measure the electric potential of the human vomeronasal organ in consequence of pheromone supply [12]. Why don't do the same experiment using a large sample of homosexual men and women? Of course many people will answer that the human sexual orientation depends on manifold factors, as social, cultural and religious, but I think that *Homo sapiens* belongs always to the class of mammals and, if the vomeronasal organ is actually involved in human sexual behavior, a meaningful number of homosexuals will be able to recognize the pheromone produced by the same sex, but not that produced by the opposite. What's more, the measure will be expressed not using an arbitrary pleasantness scale, but in millivolts.

A recent research demonstrates that male mice with a homozygous deficiency in a receptor of the vomeronasal organ mount both females and other males [17]. Besides a linkage between vomeronasal organ and homosexuality in humans could explain the meaning of many experimental data. For instance the small (i.e. feminine) dimension of the third interstitial nucleus of the anterior hypothalamus of homosexual men [18]: it could be one of the nuclei of the vomeronasal system, which in rodents is sexually dimorphic. Also the association of markers on X chromosome and the male homosexual orientation [19]: perhaps loci of regulatory or structural genes of the vomeronasal system? Also that the sex hormone levels which the fetus is subjected to are important for the future sexual orientation of the adult [20]: the genes of man and woman are essentially the same; then it is acceptable that every individual has the genes needed for forming both a "masculine" and a "feminine" vomeronasal system: the choice between one or the other could be controlled by the hormonal levels in the prenatal period. Besides the idea is not new that an individual can have the genes for both "mating types" and expresses just one of them: it's just what happens in yeast.

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