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Kallmann Syndrome and the Link between Olfactory and Reproductive Development

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The sense of smell mediates communication with the external environment through the recognition of chemical cues. In mammals, olfactory chemosensation begins in sensory neurons located in the olfactory epithelium, which lines the olfactory turbinates inside the nose, and in the epithelium of the vomeronasal organ (VNO), a tubular structure that opens on the ventral aspect of the nasal septum. Neurons in the olfactory epithelium detect volatile odorants, providing information about the external milieu, whereas sensory neurons located in the VNO detect pheromones, nonvolatile chemical signals that trigger innate and stereotyped reproductive and social behaviors, as well as neuroendocrine changes. Olfactory and vomeronasal neurons project their axons to the main and the accessory olfactory bulbs, respectively, where they synapse with dendrites of mitral and tufted cells in specialized structures called "glomeruli" (Farbman 1992). The presence of a potentially functional VNO in humans has been recently documented, but whether humans use this system to process and to respond to chemical signals emitted by other members of the species remains controversial (Dulac and Axel 1995; Berliner et al. 1996; Herrada and Dulac 1997; Monti-Bloch et al. 1998; Stern and McClintock 1998). However, regardless of the role of the VNO as a sensory organ in our species, it is now clear from the study of the X-linked disorder Kallmann syndrome (MIM 308700, MIM 147950, and MIM 244200) that development of the olfactory and vomeronasal system is required for normal sexual maturation. Here, I review studies by neurobiologists, particularly those working in the developing chick, as well as the human genetic analysis that has brought this surprising connection to light.

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Development of the Olfactory System

The olfactory system is unique in several respects and has received a great deal of attention from developmental neurobiologists in recent years. Olfactory sensory neurons continue to be regenerated from stem cells in the neuroepithelium during adult life—a rare example of persistent neurogenesis in mammals (Monti Graziadei and Graziadei 1979). Thus, the mechanisms that govern the precise pattern of projections of olfactory axons to the forebrain must operate throughout a lifetime. Furthermore, projections of olfactory neurons occur in a stereotyped manner: a series of elegant experiments demonstrated that the olfactory neurons that express a given receptor for some specific odorant all converge to a small number of glomeruli in the bulb, despite being scattered, apparently randomly, within one of four areas in the olfactory epithelium (Mombaerts et al. 1996). Guidance cues, therefore, must be present in the olfactory epithelium and in the olfactory bulb to mediate migration to the forebrain, recognition and invasion of the target, and, ultimately, the establishment of a refined spatial map (for review, see Lin and Ngai 1999).

Beside giving rise to the primary olfactory sensory neurons, the olfactory epithelium generates a population of migrating neuroblasts, which ultimately reside in the hypothalamus (Schwanzel-Fukuda and Pfaff 1989; Wray et al. 1989). In the adult, these neurons secrete gonadotropin-releasing hormone (GnRH), the key brain-peptide hormone in vertebrates that controls the synthesis and the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gonadotropes. In all vertebrate species in which the matter has been examined, GnRH neurons originate in the olfactory placode and migrate, during embryonic development, into the forebrain, along branches of the vomeronasal nerve (Schwanzel-Fukuda and Pfaff 1990). Both the amino-acid sequence of GnRH and the developmental origin of the neurons producing this peptide have been essentially conserved throughout 500 million years of vertebrate evolution.

Although extensive neuronal migration characterizes development of the entire CNS, GnRH neurons are ex-

traordinary because they are the only CNS neurons that are born peripherally and so require a mechanism of entry into the developing brain. Very little is known about the factors that modulate the migration of GnRH neurons from the olfactory placode to the hypothalamus. It is still a matter of debate whether specific cues are required to promote GnRH migration to the brain, or whether this migration is only dependent on the presence of successful connections between the brain and the olfactory nerves. To be sure, GnRH migration has been shown to occur preferentially along axons, since, in the absence of the route provided by the vomeronasal nerve, these neurons are able to migrate on the ophthalmic branch of the trigeminal nerve (Murakami et al. 1998). Cell-adhesion molecules (CAMs) expressed on the vomeronasal axons likely play an important role in promoting GnRH migration (Norgren and Brackenbury 1993). Indeed, GnRH neurons show a strong preference for migrating in association with axonal bundles that express a polysialic acid-rich (PSA) form of NCAM, and enzymatic removal of PSA strongly inhibits GnRH migration (Yoshida et al. 1999). Surprisingly, however, recent studies on NCAM and NCAM-180 knock-out mice showed that migration of GnRH neurons was not overtly affected, although in NCAM-180 mutants there was a tendency for PSA to be associated with NCAM-140 and for GnRH neurons to migrate along these fascicles (Yoshida et al. 1999).

Insights from a Human Genetic Disease: Kallmann Syndrome

That some interplay might exist between olfaction and reproduction was recognized almost 50 years ago by de Morsier, who described under the term "olfactogenital dysplasia" several cases of hypogonadism and inability to smell (anosmia), often in association with a number of median cranioencephalic dysraphias (de Morsier 1954). The genetic nature of this condition was postulated by Kallmann and colleagues in 1944, and since then the eponym Kallmann syndrome (KS) has labeled any human syndrome characterized by the association of hypogonadotropic hypogonadism and anosmia (Kallmann et al. 1944). Although this condition is genetically heterogeneous, with both autosomal and X-linked forms, only the latter is now understood at the molecular level.

The first hint of the biological explanation behind the association of hypogonadism and anosmia came when the origin of GnRH neurons from the olfactory placode was disclosed. The hypothesis could then be made that KS was the result of a defect in migration of olfactory nerves and GnRH neurons. Confirmation came from the anatomo-pathological examination of a 19-week-old human fetus affected by KS (Schwanzel-Fukuda et al. 1989). In this fetus, the olfactory, vomeronasal, and terminalis nerves were not in contact with the brain, but terminated their migration within the meninges in an abnormal neural tangle. Moreover, GnRH neurons failed to enter the brain and were found in the nasal cavities and on the dorsal surface of the cribriform plate in the above-mentioned tangle. The olfactory bulbs and tracts were absent on both sides (fig. 1). Olfactory-bulb and -tract aplasia or hypoplasia is a consistent neuroradiological findings in patients with KS. Nuclear magnetic resonance imaging in these patients detects a characteristic absence or reduction in the size of the olfactory bulb and the olfactory sulci (Bick and Ballabio 1993). The abnormal neural tangle, observed in the fetus with KS by Schwanzel-Fukuda et al. (1989), is also a frequent NMR finding in adult patients. The major symptoms of KS, hypogonadism and anosmia, can therefore be reconciled and explained as a defect in normal olfactory-system development.

An additional piece of the puzzle came to light with the cloning, in 1991, of the gene responsible for the X-linked form of Kallmann syndrome (Franco et al. 1991; Legouis et al. 1991). The *KAL* gene encodes a 680-amino-acid–secreted molecule containing protein motifs characteristic of axonal guidance factors. The amino-terminal part of the protein contains a cysteine-rich motif, a four-disulfide core domain similar to structures previously described in serine-protease inhibitors and neurophysins (Drenth et al. 1980). Although the function of this domain is currently unknown, antiprotease activity is an intriguing possibility, since nerve-growth cones express proteases on their surface to facilitate migration through the extracellular matrix (McGuire and Seeds 1990; Letourneau et al. 1992). Protease inhibitors increasingly have been shown to play an important role in neuronal migration, by controlling degradation of matrix components, as recently demonstrated in the case of the serpin family (Osterwalder et al. 1996). The carboxy-terminal two-thirds of KAL contains three FNIII repeats, adhesive motifs typical of extracellular matrix molecules, several of which have been shown to have a role in processes of neuronal migration and axonal targeting (Hynes and Lander 1992; Tessier-Lavigne and Goodman 1996). Other FNIII-repeat–containing cell-adhesion proteins also have been implicated in human genetic diseases. For example, L1CAM has been proved to be responsible for X-linked hydrocephalus, another human neuronal migration defect (Kamiguchi et al. 1998).

Mutation-detection studies in families in which KS segregates as an X-linked trait indicate a high degree of heterogeneity of mutations, although the same missense mutation, consisting of a G→A substitution at codon 514 turning glutamic acid into lysine, was recently identified in six unrelated patients of the same ethnic origin (for

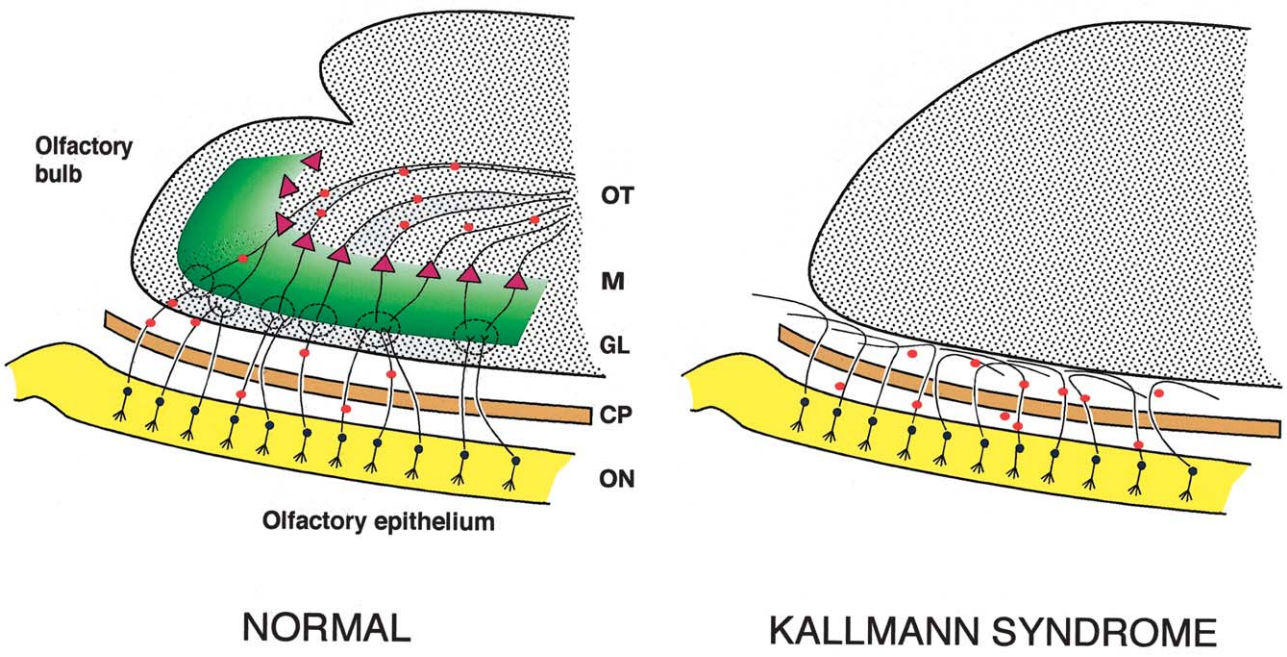

Figure 1 Model for KS pathogenesis. In normal individuals (left), the olfactory neurons (ON) in the olfactory epithelium send their axons through the cribriform plate (CP) to reach the olfactory bulb. Within the glomerular layer (GL) of the bulb, they make synapses with dendrites of mitral cells (M) whose axons will form the olfactory tract (OT). Neurons secreting GnRH (shown in red) originate in the olfactory placode and migrate along the olfactory nerves until they reach the forebrain. For simplicity, no distinction is made in this drawing between the proper olfactory nerve and the vomeronasal nerve. The KAL protein (green area) is secreted by mitral cells in the extracellular matrix of the bulb where it is required for proper interactions with olfactory axons. In KS patients (right), the KAL protein is absent, and, therefore, olfactory axons cannot interact properly with their target, ending their migration between the cribriform plate and the forebrain. The migration defect of GnRH neurons in KS is thus a secondary effect caused by lack of contact between the olfactory nerves and the forebrain, resulting in the absence of a neural migration route. (Modified from Rugarli and Ballabio [1993].)

reviews, see Ballabio and Zoghbi [1995] and Ballabio and Rugarli [in press]). Several stop-codon mutations were identified, probably resulting in a complete loss of function of KAL protein. In some patients, missense and splice-site mutations were identified, in regions of putative functional importance, on the basis of sequence-homology data. Some of the patients in whom point mutations were identified displayed, in addition to KS, mirror movements, pes cavus, high arched palate, and unilateral renal aplasia, indicating that KAL plays a role in various developmental systems (Hardelin et al. 1993). However, patients with KS who also manifest ichthyosis, chondrodysplasia punctata, mental retardation, short stature, and ocular albinism are affected by a contiguous-gene syndrome caused by deletions of the distal short arm of the human X chromosome (Ballabio and Andria 1992).

As would be predicted, given its evident importance in guiding olfactory axons and GnRH neurons to the brain, KAL is expressed in the target tissue of olfactory axons. KAL-expression studies were conducted in the chick (Legouis et al. 1993; Rugarli et al. 1993), and were confirmed in humans on fetal autoptic material (Lutz et al. 1994). During chick development, olfactory axons reach the forebrain at embryonic day 4.5 (E4.5) and, although a small number of pioneer olfactory axons transiently penetrate into the telencephalon, the vast majority accumulate outside the CNS without entering. An analogous pause in migration has been reported for GnRH neurons (Drapkin and Silverman 1999). Both olfactory axons and GnRH neurons start to invade the target tissue at approximately E6.5. Strikingly, KALc transcripts are up-regulated in the neuroepithelium of the presumptive olfactory bulb at this stage. Consistent with its role in olfactory axon pathfinding, KAL expression is maintained throughout a lifetime. Within the chick olfactory bulb, KAL is restricted to mitral cells, the secondary neurons of the olfactory pathway (Legouis et al. 1993; Rugarli et al. 1993). KALc transcription is never detectable in the olfactory epithelium or in the mesenchymal tissue, through which the olfactory axons and the GnRH neurons migrate. Altogether, these data suggest that KAL is one of the guidance cues, expressed by the olfactory bulb, that is important for olfactory axon targeting and, directly or indirectly, for GnRH migration.

Investigating KAL Function In Vitro

Although these data pointed to KAL as a key factor, produced by the olfactory bulb, that mediates successful innervation, the mechanism by which KAL acts has proved difficult to elucidate. Hypotheses for the function of KAL include roles as an adhesive molecule that provides a substrate for elongating neurites during their ultimate approach to the target, as a diffusible chemoattractant involved in pathfinding olfactory axons through the meninges to the olfactory bulb, and as a pro-invasive factor required within the olfactory bulb for target recognition by the olfactory axons. The biochemical characteristics of KAL are appropriate for any of these functions. KAL is a glycosylated protein (Rugarli et al. 1996; Soussi-Yanicostas et al. 1996), secreted in the extracellular matrix, where it binds to heparan-sulfate glycosaminoglycans (Soussi Yanicostas et al. 1996). In cell-expression systems, KAL, like other FNIII-repeat–containing proteins, undergoes proteolytic cleavage to yield a diffusible component (Rugarli et al. 1996; Soussi-Yanicostas et al. 1996). The relevance of this conversion is still controversial, since it has been observed only in cell-culture conditions.

Attempts to demonstrate a role of KAL in vitro have been largely inconclusive. So far, we have not been able to demonstrate that KAL can act at a distance to attract olfactory axon growth (S. Colamarino and E. I. Rugarli, unpublished data). A recent study has shown that an artificial substratum, composed of KAL, serves as an adhesive substrate for different cell lines and that this adhesive property is dependent on the presence of heparan sulfate and chondroitin-sulfate glycosaminoglycans on the cell surfaces (Soussi-Yanicostas et al. 1998). Moreover, the same study found that such a substratum is permissive for neurite outgrowth of mouse cerebellar neurons. These effects are mediated by a conserved 32-amino-acid peptide located in the first FNIII repeat. Although these results are encouraging and, for the first time, demonstrate a role of KAL in modulation of neurite outgrowth, they are somehow far from representing the whole story. Interestingly, these authors report that cerebellar neurite outgrowth is substantially *reduced* when the neurons were cultured on KAL-producing CHO cells, compared to wild-type CHO cells, and that cerebellar explants cultured on KAL-producing CHO cells show extensive fasciculation (Soussi-Yanicostas et al. 1998). Although this effect is in apparent contrast to the permissive role in neurite outgrowth mentioned above, one possible interpretation for these data is that uniform concentrations of KAL may stimulate axon growth, but local high concentrations caused by a discontinuous substrate (such as may be expected on cell surfaces) can induce growth cessation. This last situation more closely mimics what occurs in vivo, where olfactory axons are confronted with a sharp boundary of KAL-expressing cells when they reach the presumptive olfactory bulb, perhaps suggesting that KAL could act as a target-derived stop signal for olfactory axons.

Concluding Remarks

Although elusive, the pathogenesis of Kallmann syndrome continues to be a fascinating story. Several critical issues still need to be addressed. For instance, expression studies confirm that KAL is expressed in the developing olfactory bulb but also have revealed that in human embryos, unlike in developing chicks, KAL is transcribed by granule cells of the olfactory bulb and the cerebellum (Lutz et al. 1994). Since KAL is a secreted molecule, the significance of this difference is still unclear. Moreover, patients with Kallmann syndrome often display additional symptoms, apart from anosmia and hypogonadism, such as synkinesia, cerebellar abnormalities, and unilateral renal aplasia (Ballabio and Zoghbi 1995). In the chick, KAL is expressed in several tissues outside the olfactory bulb, some of which correlate nicely with phenotypes of patients with KS (Rugarli et al. 1993; Legouis et al. 1994), but the function of the protein in these tissues is obscure. Finally, whether KAL is directly implicated in guiding GnRH neurons into the brain is still uncertain. We favor the view that defective migration of GnRH neurons in KS is secondary to the lack of physical support provided by vomeronasal axons.

A great limitation in exploring KAL function is the lack of a mouse model for Kallmann syndrome. In fact, despite intense efforts, no murine *KAL* homologue has yet been identified. Given the extremely high conservation of olfactory-system development from fish to mammals, and the high percentage of homology between the human and the avian KAL genes, the failure to clone a mouse KAL gene may at first seem rather surprising. However, several of the human genes located on chromosome Xp22.3 are only poorly conserved with rodent genes, due to the peculiar evolutionary history of this region of the mammalian X chromosome. We hope that future information in KAL function will come through the isolation of the KAL gene in other animal models that are amenable to functional studies, such as zebrafish and *Caenorhabditis elegans*. Finally, the cloning of the genes responsible for the autosomal forms of the disease is predicted to shed more light on the neurogenic pathways that are ultimately responsible for both olfaction and gonadal development.

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Electronic-Database Information

Accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for Kallmann Syndrome 1 [MIM 308700], Kallmann Syndrome 2 [MIM 147950], and Kallmann Syndrome 3 [244200])

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