<Further Development 18_02>

Kallmann Syndrome

In the late nineteenth century, the Johns Hopkins University professor John Mackenzie (1898); the German psychiatrist, Wilhelm Fliess (1897); and the Viennese sexologist, Richard von Krafft-Ebing (1886), all shared the mistaken view that there were similarities in the development of the penis and the nose. All three of these investigators used the same case study as evidence: the report of a man who had no sense of smell–no nasal or olfactory nerves–and whose genitalia were much smaller than normal.

Such people are now known to have Kallmann syndrome, an X-linked disease characterized by anosmia (no sense of smell), small genitalia, and sterile gonads. The anosmia is due to the lack of neurons in the brain that receive input from the axons coming from nasal neurons. The small gonads and genitalia are the result of a lack of gonadotropin-releasing hormone (GnRH). GnRH is a peptide hormone secreted by the hypothalamus that instructs the anterior pituitary to secrete luteinizing hormone, the hormone required for gonadal development and genital maturation. What links these two problems? In 1989, two laboratories (Schwanzel-Fukada and Pfaff, 1989; Wray et al., 1989) made the surprising discovery that the GnRH-secreting neurons do not originate in the hypothalamus. Rather, they originate in the olfactory epithelium (the vomeronasal organ) in the nose rudiment and migrate into the hypothalamic region of the brain during fetal development (Figure 1). The olfactory receptor neurons of the nose originate from the same place. The axons from the olfactory receptor neurons enter the brain to synapse with the olfactory bulb, while the cell bodies of these neurons remain in the developing nose. Patients with Kallmann syndrome have no olfactory bulb in the brain, as the development of this bulb requires innervation from the olfactory receptor neurons (Stout and Gradziadi, 1980).

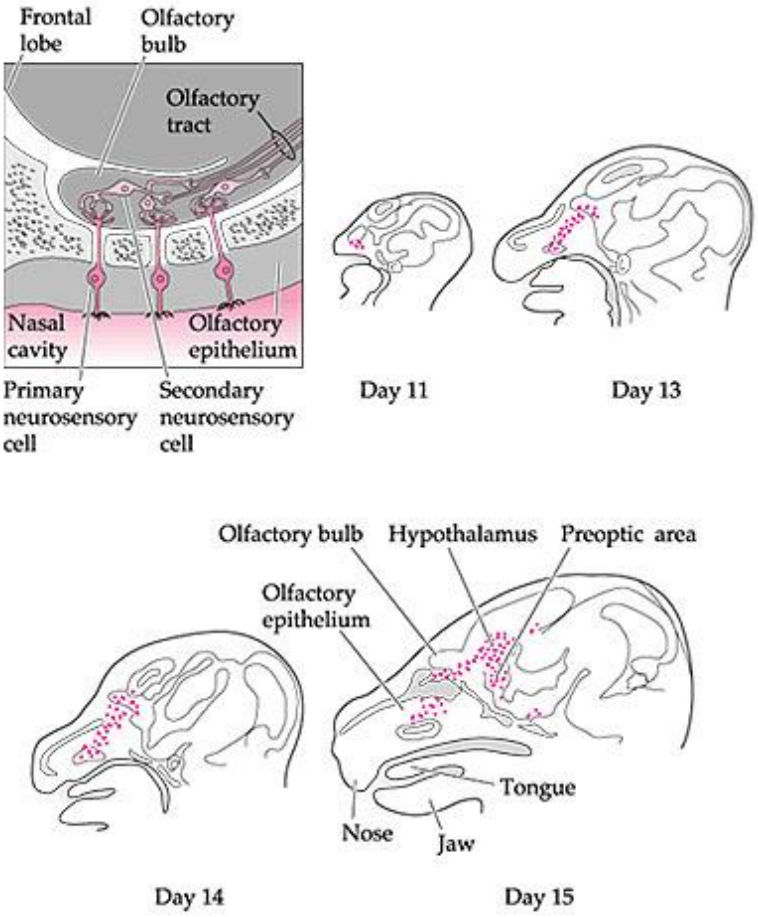

Figure 1 Model for the etiology of Kallmann syndrome. In the left illustration, sensory neurons from the olfactory epithelium extend axons into the olfactory bulb of the brain. In Kallmann syndrome, the olfactory bulb has degenerated, and this loss is thought to be secondary to the lack of axons from the sensory neurons. The series of sagittal head sections from embryonic mice shows the migration of GnRH-secreting neurons (color) from the nose anlage into the hypothalamic portion of the brain. This migration does not occur in Kallmann syndrome. (After Calof, 1992.)

The defect in Kallmann syndrome can be traced to the failure of the GnRH-secreting neurons and the olfactory neuron growth cones to migrate into the brain from the olfactory placode (Schwanzel-Fukada et al. 1989). It is thought that the olfactory axons migrate first and that the GnRH-secreting neurons follow the olfactory nerve fascicles into the brain (Livne et al. 1993). The gene, *KAL-1*, whose absence or abnormality causes the syndrome, has been cloned, and it encodes anosmin-1, a protein whose expression is detected in the basement membranes and/or interstitial matrices of several organs, including the olfactory system (Franco et al. 1991; Legouis et al. 1991; Hardelin et al. 1999). In the olfactory system, anosmin-1 was detected from week 5 onward. The protein was restricted to the developing olfactory bulbs and to the medial walls of the primitive cerebral hemispheres (i.e., along the rostro-caudal migratory pathway of the GnRH-synthesizing neurons). Anosmin is critical in the branching and extension of the olfactory bulb output neurons, and antibodies to this protein block these functions (Soussi-Yanicostas et al. 2002). It is probable that anosmin interacts with FGF receptors to mediate the effects of those growth factors (Murcia-Belmonte et al. 2010). The detection of anosmin-1 expression in the ureter bud could also explain the renal aplasia observed in about one third of the affected individuals.

An updated history of Kallmann syndrome research can be found in the Online Mendelian Inheritance in Man database.

Literature Cited

Calof, A. L. 1992. Sex, nose, and genotype. *Curr. Biol.* 2: 103–105.

Fliess, W. 1897. Quoted in J. Geller, 1992. The cultural construction of the other. In H. Eilberg-Schwartz (ed.), *People of the Body.* State University of New York Press, Albany, pp. 243–282.

Franco, B. and fifteen others. 1991. A gene deleted in Kallmann's syndrome shares homology with neural cell adhesion and axonal path-finding molecules. *Nature* 353: 529–536.

Hardelin J. P., Julliard, A. K., Moniot, B., Soussi-Yanicostas, N., Verney, C., Schwanzel-Fukuda, M., Ayer-Le Lievre, C., and Petit, C. 1999. Anosmin-1 is a regionally restricted component of basement membranes and interstitial matrices during organogenesis: implications for the developmental anomalies of X chromosome-linked Kallmann syndrome. *Dev Dyn*. 215: 26–44.

Krafft-Ebing, R. von. 1886. *Psychopathia Sexualis.* Enke, Stuttgart.

Legouis, R. and fourteen others. 1991. The candidate gene for X-linked Kallmann syndrome encodes a protein related to adhesion molecules. *Cell* 67: 423–435.

Livne, I., Gibson, M. J. and Silverman, A. J. 1993. Biochemical differentiation and intercellular interactions of migratory GnRH cells in the mouse. *Dev. Biol.* 159: 643–666.

Mackenzie, J. L. 1898. The physiological and pathological relations between the nose and the sexual apparatus of man. *Johns Hopkins Hosp. Bull.* 82: 10–17.

Murcia-Belmonte, V., P. F. Esteban, D. García-González and F. de Castro. 2010. Biochemical dissection of Anosmin-1 interaction with FGFR1 and components of the extracellular matrix. *J. Neurochem*. 115: 1256–1265.

Schwanzel-Fukada, M. and Pfaff, D. W. 1989. Origin of luteinizing hormone-releasing hormone neurons. *Nature* 338: 161–164.

Schwanzel-Fukada, M., Bick, D. and Pfaff, D. W. 1989. Luteinizing hormone-releasing hormone (LHRH)-expressing cells do not migrate normally in an inherited hypogonadal (Kallman) syndrome. *Mol. Brain Res.* 6: 311–326.

Soussi-Yanicostas, N., F. de Castro, A. K. Julliard, I. Perfettini, A. Chédotal and C. Petit. 2002. Anosmin-1, defective in the X-linked form of Kallmann syndrome, promotes axonal branch formation from olfactory bulb output neurons. *Cell* 109: 217–228.

Stout, R. P. and Gradziadi, P. P. C. 1980. Influence of the olfactory placode on the development of the brain in Xenopus laevis (Daudin). *Neuroscience* 5: 2175–2186.

Wray, S., Grant, P. and Gainer, H. 1989. Evidence that cells expressing luteinizing hormone-releasing hormone mRNA in the mouse are derived from progenitor cells on the olfactory placode. *Proc. Natl. Acad. Sci.* USA 86: 8132–8136.