Growth hormone found to have new role in development of brain's smell center

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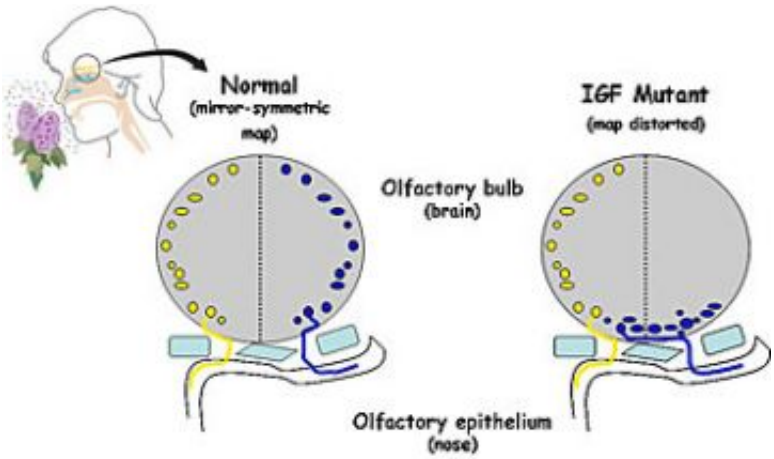

Airborne scent chemicals (inset) stimulate odor receptors in the nasal cavity, which send signals to the brain's olfactory bulb (yellow) located in the frontal lobe of the brain just above the nasal bone. These connections are set up during early development when sensory nerves in the nose send axons into the brain (blue and gold) that target specific neurons in the bulb to create a map of sensory information that displays a mirror symmetry across the bulb's midline (dashed line). When IGF signaling is disrupted (right), the blue axons collapse toward the bulb's midline, resulting in a distortion of this sensory map, demonstrating the critical role played by IGF in wiring the brain. (John Ngai/UC Berkeley; inset courtesy Nobel prize committee)

A human hormone known to stimulate the growth of cells throughout the body has a new role - helping to set up the proper nerve connections in the odor center of the brain, according to University of California,

Berkeley, scientists.

The hormone, insulin-like growth factor (IGF), is well-known to biomedical researchers and has been tested as a therapy for diabetes and some growth disorders. Until now, decades of research have turned up only one solid role for IGF, however, and that is to makes cells grow and multiply.

Neuroscientist John Ngai, Coates Family Professor of Neuroscience and director of the Functional Genomics Laboratory at UC Berkeley, and his colleagues have now found that IGF plays a critical role in setting up the connections between chemical detectors in the nose and the brain's olfactory centers. These centers, the olfactory bulbs, are a pair of raisin-sized structures in the front part of the brain that analyze signals from the many odor receptors in the nose.

IGF joins a small number of identified molecules known to direct the growth of nerve cells in the brain during its development, making it "another tool in the brain's tool kit for how you wire up the brain," Ngai said.

Aside from what this reveals about how the brain wires itself as it grows, these molecules could become important therapeutically once doctors begin implanting new cells, perhaps stem cells, into the brain to cure neurodegenerative diseases, Ngai said.

"Even if you figure out a way to grow new cells to replace dying cells, those cells still need to make proper connections," Ngai said. "So, anything you know about what drives normal connectivity in the brain will help you figure out how to get those new cells to wire up correctly."

Ngai and colleagues at UC Berkeley, the Shanghai Institutes of Biological Sciences in China and Columbia University Medical Center

reported their findings in the March 27 issue of the journal *Neuron*.

The molecules netrin, ephrin, semaphorin, slit and now IGF are called axon guidance molecules because as nerves stretch their tentacle-like axons out into the brain to connect with other neurons, these molecules act as signposts to steer the axons to the correct brain cells. As the brain grows during early development to some 3 billion nerve cells, each nerve cell makes, on average, 10,000 connections with other nerve cells, so "guidance cues" are critical.

"Cells from the retina of the eye, for example, carry signals into your brain conveying information about the outside world, and these go back into your brain in a very ordered projection such that there is a topographic map of the visual world from the retina at each successive layer of relays in the brain," Ngai said. "Something must order those connections, or otherwise you wouldn't be seeing a coherent image."

So far, these axon guidance cues include chemoattractants that make axons grow toward them, and chemorepellants, which make them turn away. As shown by Ngai's colleagues in China, IGF is an attractant; the growth cones of axons turn toward higher concentrations of the hormone.

Compared to the visual system, the brain's odor system is still poorly understood, but it appears to have its own uniquely ordered connections, Ngai said. The nose contains some 5 million nerve cells, each of which carries only one kind of odor receptor out of about 1,000 different odor receptors, each tuned to detect different chemicals or odorants. Nose nerve cells that detect the same odorant send their axons to the same region of the olfactory bulb, and it appears that neurons that detect similar chemicals, such as different alcohols, send their axons to nearby areas of the bulb.

Scientists previously had discovered that each of our two olfactory bulbs is divided down the middle between two mirror-image representations of the nasal odor receptors. Ngai and his colleagues found that IGF is responsible for setting up these mirror images within the bulb.

"IGF signaling is absolutely required for this mirror symmetry," he said. "In the absence of IGF function, you lose information from the sensory axons of the nose to one half of the bulb."

Axons from the nose appear to express receptors for IGF on their growth cones, which allow the growth cones to essentially sniff out the IGF in the olfactory bulb and follow the trail to the proper target cells. Without the IGF produced in the olfactory bulb, the growing axons do not make the turn-off to the outer half of each bulb, but instead go only to the inner side nearest the midline of the brain.

Both of the IGF protein's forms, dubbed IGF-1 and IGF-2, are expressed by cells in the olfactory bulb, as determined by DNA microarray screens and other techniques.

While IGF appears critical in the early stages of olfactory development, when the basic architecture of the olfactory bulb is being set up in the fetus and perhaps also after birth, other axon guidance cues are no doubt needed to more finely direct the growth of axons, Ngai said. He is continuing to investigate these other cues, and also to map the nose's chemical receptors to specific areas of the bulb. Ngai and his colleagues also are following up on some early leads indicating that IGF may serve as a chemoattractant in other parts of the developing brain.

"We are seeing an emerging picture with IGF," Ngai said. "Over the past three years, there have been studies from others showing a role for IGF signaling in establishing the shape of certain neurons, and other studies showed that IGF is required for how fast axons grow. The present study

tells us that IGF is actually being used as a chemoattractant. This is a new role for IGF in development."

Source: University of California - Berkeley

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