A ventral glomerular deficit in Par kinson ’ s disease revealed by whole olfactory bulb reconstruction

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Abstract

Olfactory dysfunction is common in Parkinson’s disease and is an early symptom, but its pathogenesis remains poorly understood. Hindering progress in our mechanistic understanding of olfactory dysfunction in Parkinson’s disease is the paucity of literature about the human olfactory bulb, both from normal and Parkinson’s disease cases. Qualitatively it is well established that the neat arrangement of the glomerular array seen in the mouse olfactory bulb is missing in humans. But rigorous quantitative approaches to describe and compare the thousands of glomeruli in the human olfactory bulb are not available. Here we report a quantitative approach to describe the glomerular component of the human olfactory bulb and its application to draw statistical comparisons between olfactory bulbs from normal and Parkinsonıs disease cases. We subjected horizontal 10 εm sections of olfactory bulbs from six normal and ýve Parkinsonıs disease cases to þuorescence immunohistochemistry with antibodies against vesicular glutamate transporter-2 and neural cell adhesion molecule. We scanned the immunostained sections with a þuorescence slide scanner, segmented the glomeruli and generated 3D reconstructions of whole olfactory bulbs. We document the occurrence of atypical glomerular morphologies and glomerular-like structures deep in the olfactory bulb, both in normal and Parkinsonıs disease cases. We deýne a novel and objective parameter: the global glomerular voxel volume, which is the total volume of all voxels that are classiýed immunohistochemically as glomerular. We ýnd that the global glomerular voxel volume in Parkinsonıs disease cases is half that of normal cases. The distribution of glomerular voxels along the dorsal-ventral dimension of the olfactory bulb in these series of horizontal sections is signiýcantly altered in Parkinsonıs disease cases: whereas most glomerular voxels reside within the ventral half of olfactory bulbs from normal cases, glomerular voxels are more evenly spread among the ventral and dorsal halves of olfactory bulbs from Parkinson’s disease cases. These quantitative whole-olfactory bulb analyses indicate a predominantly ventral deýcit in the glomerular component in Parkinsonıs disease, consistent with the olfactory vector hypothesis for the pathogenesis of this neurodegenerative disease. The distribution of serine 129-phosphorylated alpha-synuclein immunoreactive voxels correlates with that of glomerular voxels. The higher the serine 129-phosphorylated alpha-synuclein load of an olfactory bulb from a Parkinson’s disease case, the lower the global glomerular voxel volume. Our rigorous quantitative approach to the whole olfactory bulb will help understand the anatomy and histology of the normal human olfactory bulb and its pathological alterations in Parkinson’s disease.

Biography

Peter Mombaerts was born in 1962 in Leuven, Belgium. He obtained his M.D. degree in 1987 at the Catholic University of Leuven. He then joined the laboratory of Dr. Susumu Tonegawa at MIT, Cambridge, MA, USA, where he obtained his Ph.D. degree in 1992 with a thesis on immunodeýcient mice generated by gene targeting. As a postdoc with Dr. Richard Axel at Columbia University, New York, NY, USA (1993-1995), he developed a genetic approach to visualize axonal projections of mouse olfactory sensory neurons that express the same odorant receptor gene. From 1995-2007 he was faculty member at The Rockefeller University in New York, NY, USA. In 2008 he moved to Frankfurt as director of the newly created Department of Molecular Neurogenetics at the Max Planck Institute of Biophysics. In 2013 he became the director of the independent Max Planck Research Unit of Neurogenetics. He has authored 125 papers, which have been cited 18,000 times.

Publications

1. Generation of differentiated tissue from nuclear transfer embryonic stem cells and methods of use
2. Expert curation of the human and mouse olfactory receptor gene repertoires identiýes conserved coding regions split across two exons.
3. A transcriptomic atlas of mammalian olfactory mucosae reveals an evolutionary inþuence on food odor detection in humans.
4. Onset of TCR-beta gene rearrangement and role of TCR-beta expression during CD3-CD4-CD8-thymocyte differentiation.
5. Method to produce cloned embryos and adults from cultured cellsf

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