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A GUT-BRAIN NEURAL CIRCUIT

A hallmark of Parkinson's disease (PD) is the accumulation of intracellular aggregates containing the neuronal protein α -synuclein known as Lewy bodies. Clinical and pathological evidence indicates that abnormal α -synuclein is found in enteric nerves before it appears in the brain. It has been proposed that misfolded α -synuclein can form fibrils that may spread from one neuron to another in a prion-like fashion eventually reaching the brain. However, it is not known whether misfolding of α -synuclein in enteric nerves is the initiating event in the development of PD or whether other cells may be involved. Enteroendocrine cells (EECs) are sensory cells of the gastrointestinal tract and reside in the mucosal surface of the gut where they are exposed to nutrients and other ingested substances. Our laboratory discovered that many EECs possess basal cytoplasmic processes called neuropods that contain neurofilaments, synaptic proteins, and small, clear secretory vesicles that are believed to contain neurotransmitters. Thus, in many ways, EECs resemble neurons. Since the discovery of neuropods, we found that EECs also contain α -synuclein. Finally, we discovered that EECs form a synaptic connection with enteric nerves, thus providing a route from the lumen of the gut to the nervous system. These findings identify a previously unrecognized location where PD-associated changes to α -synuclein may occur and raise the possibility that environmental influences in the gut induce misfolded α -synuclein in the gut epithelium that spreads to the enteric nervous system and then to the CNS.

Biography

Rodger Liddle is Professor of Medicine at the Duke University. Our laboratory has had a longstanding interest in two types of EECs that regulate satiety and signal the brain to stop eating. Cholecystokinin (CCK) is secreted from EECs of the upper small intestine and regulates the ingestion and digestion of food through effects on the stomach, gallbladder, pancreas and brain. Peptide YY (PYY) is secreted from EECs of the small intestine and colon and regulates satiety. We recently demonstrated that CCK and PYY cells not only secrete hormones but are directly connected to nerves through unique cellular processes called 'neuropods'. Our laboratory is devoted to understanding EECs signaling and its role in disease.

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