# Incretin hormones and brain microglia team up to regulate brain homeostasis

The entire human body is made up of many complicated cells, processes, and interactions. As scientific discoveries are made, it becomes increasingly more evident how multidimensional and interconnected all of the biological systems and pathways of the human body really are. Incretin hormones, which include glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP), have traditionally been known for their role in balancing metabolism in the human body. These two hormones work as 'middle-men' proteins; they relay signals from the intestines to the pancreas following the ingestion of food. Once these incretin hormones have arrived at the pancreas, they stimulate the release of insulin by the pancreas. Following the secretion of insulin, glucose moves from the bloodstream into the cells and tissues that rely on glucose as a fuel source. Incretins play an important role in this process, as they help to ensure that enough insulin is secreted so that sufficient amounts of glucose can enter the body's tissues.

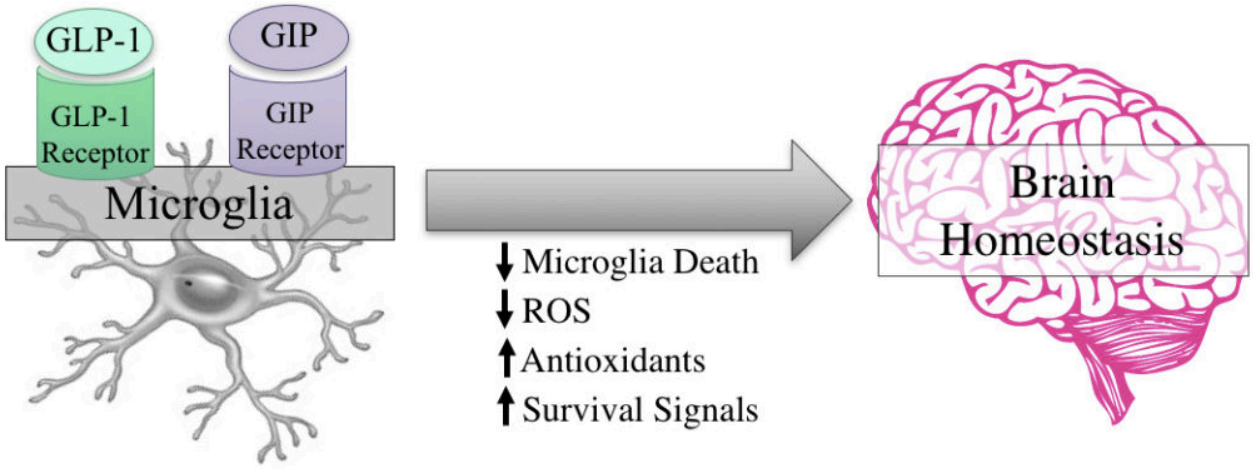


Fig. 1. GLP-1 and GIP Work with Microglia to Promote Brain Cell Survival and Homeostasis.

Recently, it has been shown that the roles of GLP-1 and GIP extend far beyond their metabolic functions in the periphery; these two incretin hormones can also prevent the death of neuronal cells, which is unmistakably essential for maintaining a brain health. However, our research further revealed that the roles of GLP-1 and GIP in the brain are vast and extend beyond protecting neurons alone. More specifically, we have discovered that these two incretin hormones display a wide array of properties on the brain, including regulating inflammation and neuroprotection, by operating on the microglia, the resident immune cells of the brain. Microglia play a critical role in maintaining balance (homeostasis) in the brain; they protect and defend against foreign invaders, respond to damage and injury signals, and provide essential chemical support to neurons.

We made the exciting discovery that human microglia express both the GLP-1 receptor and the GIP receptor, which are necessary to detect and respond to GLP-1 and GIP, respectively. We found that GLP-1 and GIP bind to, and activate, their respective receptor on the microglia. We also demonstrated that, when microglia were exposed to a specific type of toxic inflammation, the interaction between GLP-1 or GIP and their receptors prevented the otherwise eminent death of microglia cells. In addition to inhibiting the death of brain cells, GLP-1 and GIP also exert antioxidant properties in the brain. Microglia, when inflamed, produce significantly increased levels of destructive reactive oxygen species (ROS); however, the addition of GLP-1 or GIP to inflamed microglia cells drastically reduced the ROS levels, which was associated with increased levels of certain anti-oxidant hormones, such as glutathione peroxidase. These two observations are likely linked, since the beneficial antioxidant enzymes play a role in removing the toxic ROS from the human body, as well as repairing the damages caused by ROS.

In addition to producing protective effects during inflammation events in the brain, we further demonstrated that GLP-1 and GIP could be beneficial for microglia even in the absence of inflammation. When GLP-1 or GIP were added to non-inflamed microglia, these hormones caused an increase in the levels of several key brain cell survival molecules, such as brain derived neurotrophic factor, glial cell-line derived neurotrophic factor, and nerve growth factor.

Therefore, we have discovered that the incretin hormones, GLP-1 and GIP, team up with microglia to play a major role in the survival of brain cells and maintaining homeostasis in the brain.

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## Publication

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