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Effect of microglia cell activation on neuronal cells in coculture

Superoxide, O_2^- , is a free radical generated in cells and is a precursor for production of a range of reactive oxygen species (ROS). In phagocytes, O_2^- acts as a microbicidal agent for killing invading micro-organisms. However, uncontrolled O_2^- production in non-phagocytic cells can cause severe oxidative stress, resulting in extensive tissue damage and destruction. Oxidative stress is thought to be the cause of several neurodegenerative diseases, including Parkinson's, Alzheimer's and stroke. One of the sources of O_2^- is the plasma membrane enzyme NADPH-oxidase, which is comprised of a number of subunits and regulated by protein kinases. Activation of NADPH-oxidase has been implicated in oxidative stress related disease states. The central nervous system is comprised of neurons and glia (astrocytes and microglial cells). Upon oxidative insult, glial cells become activated and may release factors that are deleterious to neurons. However, the mechanism underlying activation of glial cells and neuronal death is still unknown. Since high levels of NADPH oxidase is present in both astrocytes and microglial cells, it is possible that activation of this enzyme and production of O_2^- play a role in the glial – neuron interaction. Microglial cells can be activated by endotoxin and pro-inflammatory cytokines to produce inflammatory factors such as cytokines and nitric oxide (NO). NO can react with O_2^- to form peroxynitrite ($ONOO^-$), an extremely cytotoxic compound. Recent studies by others have shown that neuronal damage by glial cells occurs when both neurons and glial cells are in close contact with each other. In this series of experiments, we tested the effects of activated microglial cells (BV-2) on retinoic acid-differentiated neuronal cells (SH-SY5Y) in coculture systems with contact and without contact. For a comparison, BV-2 and SH-SY5Y cells were treated individually. Microglial cells were stimulated with different proinflammatory cytokines known to stimulate NO production and agonists known to stimulate NADPH oxidase. We found that BV-2 cells produce NO and that membrane bound units of NADPH-oxidase are upregulated following insult. Understanding the mechanism for microglial cells to alter neuronal function will be important towards understanding many neurodegenerative disease processes.