

The presence of macronutrients in the intestinal lumen are sensed, resulting in changes in gastrointestinal function, including inhibition of gastric emptying, stimulation of pancreatic secretion and inhibition of food intake. These responses comprise the postprandial response to food designed to match the entry of nutrients with the digestive and absorptive capacity of the intestine. In addition, the presence of macronutrients, including dietary lipid, acts in the intestine to inhibit food intake. Our laboratory has determined the humoral and neural pathways mediate lipid detection in the intestinal wall and how this information is sent to the brain. The pathway involved release of gut hormones, cholecystokinin (CCK), and activation of sensory fibers in the vagus nerve, the principle autonomic nerve connecting the gut to the brain.

Recently it has been demonstrated that the vagus nerve not only is important in the regulation of GI function and food intake but also mediates an anti-inflammatory response. Stimulation of the vagus nerve has been shown to reduce release of inflammatory cytokines and reduce the changes in cardiorespiratory function in response to a number of insults, including hemorrhagic shock, sepsis and pancreatitis. Importantly, enteral fat strongly reduced systemic inflammation after hemorrhagic shock, suggesting an interaction between macronutrients and a systemic immune response. In particular, olive oil was found to be several fold more potent than fish oil in eliciting the vagal anti-inflammatory response.

The overall goal of this proposal is to understand the mechanism by which olive oil in the intestine activates the vagal anti-inflammatory reflex. The hypothesis to be tested is that olive oil, compared with fish oil or soybean oil, produces a more potent anti-inflammatory response because it is more effective in releasing CCK from gut endocrine cells, resulting in a greater activation of the vagal afferent pathway. Experiments will be performed in awake rats or mice. Oils from different sources will be perfused into the intestine and the levels of inflammatory cytokines will be determined in mesenteric lymph under control conditions and following induction of experimental sepsis. In addition, the mesenteric lymph will be injected into healthy recipient animals and the acute lung injury measured (apoptosis, myeloperoxidase levels, alveolar wall thickness). The pathways mediating the response to olive oil will be investigated using transgenic mice lacking key molecules (such as CCK, apolipoprotein A-IV) known to be involved in detection of lipid in the gut wall.

The significance of this proposal is that a greater understanding of the anti-inflammatory response to enteral olive oil will help in treatment of patients with a number of acute medical conditions. In addition, this will add to our understanding of the response of the GI tract to macronutrients and overall health.