CCK2 RECEPTOR NULLIFICATION ATTENUATES LIPOPOLYSACCHARIDE-INDUCED SICKNESS BEHAVIOR

Kent S, Weiland TJ, Voudouris, NJ

School of Psychological Science, La Trobe University, Bundoora, VIC, Australia

**Background**- Systemic infection produces a highly regulated set of responses such as fever, anorexia, adipsia, inactivity, and cachexia, collectively referred to as sickness behaviour. Although the expression of sickness behaviour requires immune-brain communication, the mechanisms by which peripheral cytokines signal the brain are unclear. Several mechanisms have been proposed for neuroimmune communication, including the interaction of cytokines with peripheral nerves. A critical role has been ascribed to the vagus nerve in mediating sickness behaviour after intraperitoneally delivered immune activation, and converging evidence suggests that this communication may involve neurochemical intermediaries afferent and/or efferent to this nerve.

**Procedure**- Mice lacking functional CCK2/gastrin receptors (CCK2KO) and wild-type (WT) controls were administered LPS (50, 500, or 2,500 µg/kg; serotype 0111:B4; ip). Changes in core body temperature (CBT), locomotor activity, body weight, and food and water intake were determined for 4 days post-injection.

**Results**- Compared with WT controls, CCK2KO mice were significantly less affected by LPS on measures except water intake across the 50-fold range of doses, with the magnitude of effects typically increasing with increasing LPS dose. For example, in CCK2KO mice the febrile response to 50 µg/kg LPS had a slower onset and the peak was only 49% of that seen in WT controls; and the peak after 500 µg/kg was only 36% of that seen in WT mice. Although the initial febrile response to the largest dose was similar, the subsequent hypothermia was larger and longer lasting in WT mice. Similarly, the cachexic effect of LPS in CCK2KO mice was only 43, 37, and 50% of that seen in WT mice at all 3 doses, respectively.

**Conclusions**- Our findings strongly indicate an involvement of CCK2 receptors in the initiation and maintenance of LPS-induced sickness behaviour. Given the doses used and the fact that most CCK2 receptors are located centrally, this has important implications regarding the possible mechanisms of action of immune-to-brain communication. Although activation of CCK2 receptors at the level of the vagus nerve cannot be excluded, a possible role for these receptors in nonvagal routes of immune-brain communication is suggested.