

## CYTOKINE SIGNALLING IN FEVER: RECENT DEVELOPMENTS

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Cytokines, are a heterogeneous family of endogenous, hydrophilic proteins, which are associated primarily with the peripheral immune system but are now known to be produced by and act on the brain. These molecules are produced in response to a variety of physiological and pathophysiological stimuli and through their actions on the brain activate an array of sickness behaviours such as fever during, for example, infection or inflammation. Interleukin (IL)-1 is the best known and first discovered member of this family (Rothwell & Luheshi, 2000). This cytokine is a potent pyrogen, which acts on hypothalamic sites to induce fever. As well as acting on the brain IL-1 has also been proposed to be the circulating pyrogen which activates its hypothalamic receptors after gaining access from the circulation to the brain. Failure to detect biologically significant levels of this cytokine in the circulation of febrile subjects however argued against such a role for IL-1. Alternative hypotheses have since been suggested, the most prominent of which indicating that neural afferent signals through the vagus nerve are involved (Watkins, Maier & Goehler, 1995). This hypothesis was arrived at with observations, largely obtained from work on rodents which demonstrated that sickness like behaviors including fever, social exploration and others, are abrogated in vagotomized animals injected systemically with infectious/inflammatory agents such as lipopolysaccharide (LPS). There is now overwhelming evidence supporting this hypothesis in generalized sickness behaviours, however our own recent experiments in rodents suggested that at least in fever a humoral factor namely the cytokine IL-6 is involved. This is supported by the fact that circulating IL-6 concentration increase dramatically following LPS administration and that this increase correlates well with the development of the febrile response in rats. More convincingly our recent studies (Cartmell *et al.*, 2000) using a neutralizing antiserum raised against rat IL-6, have shown that systemic administration of this antiserum totally abolished LPS induced fever in rats. These results support strongly a role for IL-6 as a mediator of peripheral signals to the brain during infection or inflammation induced fever. The role of IL-6 in this response and its interaction with other cytokines such as IL-1 will be discussed.

Rothwell, N.J. & Luheshi, G.N. (2000) Interleukin-1 in the brain: Biology, pathology and therapeutic target. *Trends Neurosci.* 23(12), 618-625.

Watkins, L.R., Maier, S.F. & Goehler, L.E. (1995) Cytokine-to-brain communication: a review & analysis of alternative mechanisms. *Life Sci.* 57: 1011-1026.

Cartmell, T., Poole, S., Turnbull, A.V., Rothwell, N.J. & Luheshi, G.N. (2000) Circulating interleukin (IL)-6 mediates the febrile response to localised inflammation in rats. *J.Physiol.(Lond)* 526: 653-661.

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