

The potential effect of cortistatin on endotoxic shock with

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What is Cortistatin?

Mario Delgado, Elena Gonzalez-Rey and Alejo Chorny: Cortistatin is a recently discovered cyclic neuropeptide named after its predominantly cortical expression and ability to depress cortical activity. Cortistatin shows a high homology with somatostatin; however, based on nucleotide sequence and chromosomal location they are products of separate genes. Cortistatin binds to all five cloned somatostatin receptors and share many pharmacological and functional properties with somatostatin including the depression of neuronal activity and inhibition of cell proliferation. However, cortistatin also has many distinct properties including induction of slow-wave sleep, and reduc-

tion of locomotor activity. Cortistatin, but not somatostatin, has been detected in various human immune cells, including lymphocytes, monocytes, macrophages and dendritic cells. Therefore, some of the somatostatin immunomodulatory actions could be shared by cortistatin. Because cortistatin levels correlate with the degree of inflammatory cell differentiation and activation, this peptide could function as a major endogenous regulatory factor in the immune system. In addition to somatostatin receptors, cortistatin can bind to other hormone receptors that mediate anti-inflammatory actions, such as the receptor for the growth hormone secretagogue ghrelin.

Is there any relation between Cortistatin and septic shock?

Mario Delgado, Elena Gonzalez-Rey and Alejo Chorny: Septic shock is a systemic response to severe bacterial infections, generally caused by Gram-negative bacterial endotoxins. Indeed, the administration of the endotoxin lipopolysaccharide (LPS) to experimental animals leads to pathophysiologic changes similar to human septic shock syndrome, and lethal endotoxemia has been extensively used as an experimental model of Gram-negative septic shock. The septic shock syndrome is characterized by a hyperactive and out-of-balance network of endogenous pro-inflammatory cytokines, including TNF α , IL-12, IL-6, and IFN- γ . The overproduction of inflammatory

cytokines generates systemic activation, which affects vascular permeability, cardiac function, induces metabolic changes that can lead to tissue necrosis, and eventually to multiple-organ failure and death. The current therapeutic strategies for human septic shock are designed to neutralize one or more of the inflammatory mediators, and none of them are entirely effective. This illustrates the need for novel therapeutic approaches to downregulate the exacerbated inflammatory response typical of endotoxemia.

In a recent work, we investigated the effect of cortistatin on the production of inflammatory mediators and its therapeutic action in various murine models of endotoxemia.

Cortistatin downregulated the production of inflammatory mediators by endotoxin-activated macrophages. The administration of cortistatin protected against lethality after cecal ligation and puncture, or injection of bacterial endotoxin or *Echerichia coli*, and

prevented the septic shock-associated histopathology, such as infiltration of inflammatory cells and intravascular disseminated coagulation in various target organs. The therapeutic effect of cortistatin was mediated by decreasing the local and systemic levels of a wide spectrum of inflammatory mediators, including cytokines, chemokines and acute phase proteins. Of physiological relevance is the observation that the expression of cortistatin and its receptors increases in inflammatory cells in response to immune activation, especially following inflammatory stimuli.

Do you believe that Cortistatin represents a potential multistep therapeutic agent for human septic shock?

Mario Delgado, Elena Gonzalez-Rey and Alejo Chorny: This work provides the first evidence of cortistatin as a new immunomodulatory factor with the capacity to deactivate the inflammatory response. Cortistatin represents a potential multistep therapeutic agent for human septic shock, to be used in combination

with other immunomodulatory agents, or complementary to other therapies. In addition, other recent work performed in our laboratory has demonstrated the therapeutic effect of cortistatin in an experimental model of inflammatory bowel disease, acting again as a potent anti-inflammatory factor.

REFERENCES

1. Gonzalez-Rey et al. PNAS USA 103, 4228, 2006
2. Gonzalez-Rey et al. J Exp Med 203, 563, 2006