

## Botulinum toxin type-A therapy in cluster headache: a novel molecular mechanism

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Dear Editor,

I read with great interest the article by Sostak et al. [1]. This work shows that botulinum toxin markedly suppresses cluster headache. I would like to complete the discussion of Sostak et al. [1] by introducing a major route through which botulinum toxin could suppress cluster headache.

Interleukin-1 is a potent prototypical pro-inflammatory cytokine implicated in the pathogenesis of cluster headache [2, 3]. Therefore, as described below, the botulinum toxin minimizes headache by inactivating interleukin-1.

Bacteria produce many enzymes that show extraordinary specificity for mammalian intracellular proteins. The specificity of these bacterial enzymes has not only made them a valuable tool for elucidating the cellular functions of their targets but has also increased our understanding of protein interactions [4]. *Clostridium botulinum* is no exception, producing two classes of enzymes that have very specific protein targets, neurotoxin A–G and the ADP-ribosyltransferases C2, C3 bot 1 and C3 bot 2 [4]. C2 and C3 bot are a part of a larger family of ADP-ribosylating toxins, including diphtheria toxin and cholera toxin, which cleave NAD and transfer ADP-ribose to target proteins. Although the members of this family have homologous enzymatic domains and similar active sites, these toxins ribosylate ADP and therefore, disable a range of cellular

targets [4]. Rho family GTPases control the assembly of both cell–matrix and cell–cell adhesion complexes. IL-1 receptor signaling complex contains these G proteins, and Rho GTPase is an essential unit for the activation of IL-1 inflammatory pathway. C3 transferase exoenzyme specifically inhibits Rho GTPase by ADP-ribosylation of amino acid asparagine-41 [5, 6].

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