J Headache Pain (2008) 9:133
DOI 10.1007/s10194-008-0025-y

LETTER TO THE EDITOR

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

Hamid Namazi

Received: 25 January 2008 / Accepted: 4 February 2008 / Published online: 26 February 2008

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 exonzyme specifically inhibits Rho GTPase by ADP-ribosylation of amino acid asparagine-41 [5, 6].

Reference

1. Sostak P, Krause P, Forderreuther S et al (2007) Botulinum toxin type-A therapy in cluster headache: an open study. J Headache Pain 8(4):236–241. doi:10.1007/s10194-007-0400-0
2. Martelletti P, Granata M, Giacovazzo M (1993) Serum interleukin-1 beta is increased in cluster headache. Cephalalgia 13(5):343–345
3. Martelletti P (2000) Proinflammatory pathways in cervicogenic headache. Clin Exp Rheumatol 18(2 Suppl 19):S33–38
4. Holbourn KP, Sutton JM, Shore C et al (2005) Molecular recognition of an ADP-ribosy1 transferase; clostridium C3 exoenzyme. Proc Natl Acad Sci 102(15):5357–5362
5. Harmey D, Stenbeck G, Nobes CD et al (2004) Regulation of osteoblast differentiation by pasteurella multocida toxin (PMT): a role for Rho GTPase in bone formation. J Bone Miner Res 19(4):661–667
6. Singh R, Wang B, Shirraikar A, et al (1999) The IL-1 receptor and Rho directly associate to drive cell activation inflammation. J Clin Invest 103(11):1561–1570

H. Namazi (✉)
Chamran Hospital, Shiraz University of Medical Sciences,
Shiraz, Iran
e-mail: Namazih@sums.ac.ir