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Direct central nervous system effects of botulinum neurotoxin

Matteo Caleo, Laura Restani

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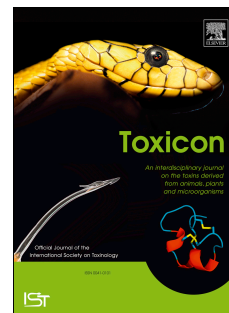
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DIRECT CENTRAL NERVOUS SYSTEM EFFECTS OF BOTULINUM NEUROTOXIN*Matteo Caleo¹ and Laura Restani^{1,*}*¹CNR Neuroscience Institute, via G. Moruzzi 1, 56124 Pisa, Italy

*Corresponding author: restani@in.cnr.it

Running title: Direct central actions of BoNT/A.**Abstract**

Local intramuscular injections of botulinum neurotoxin type A (BoNT/A) are effective in the treatment of focal dystonias, muscle spasms, and spasticity. However, not all clinical effects of BoNT/A may be explained by its action at peripheral nerve terminals. For example, the therapeutic benefit may exceed the duration of the peripheral neuroparalysis induced by the neurotoxin. In cellular and animal models, evidence demonstrates retrograde transport of catalytically active BoNT/A in projection neurons. This process of long-range trafficking is followed by transcytosis and action at second-order synapses. In humans, several physiological changes have been described following intramuscular delivery of BoNT/A. In particular, clinical studies have documented a decrease in Renshaw cell-mediated inhibition (i.e., recurrent inhibition), which may be important therapeutically for normalizing uncoordinated movements and overflow of muscle activity. In this review, we present data obtained in animal and experimental models that support direct central actions of BoNT/A mediated via retrograde axonal trafficking. We also discuss the reorganization

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