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Translocation and dissemination of botulinum neurotoxin from the intestinal tract

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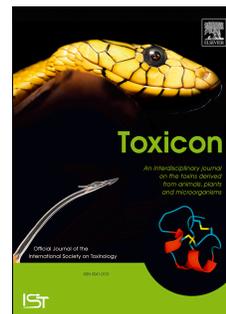
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1 **TRANSLOCATION AND DISSEMINATION OF BOTULINUM** 2 **NEUROTOXIN FROM THE INTESTINAL TRACT**

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10 **Abstract**

11 Botulinum neurotoxins (BoNTs) are potent toxins which induce flaccid paralysis by
12 inhibiting the release of acetylcholine at the neuromuscular junctions. They associate with
13 non-toxic proteins (ANTPs or NAPs) to form complexes of various sizes which are resistant
14 to acidic pH and protease degradation. BoNT trafficking from the digestive tract to the target
15 neurons is still a matter of debate. BoNTs use different strategies to pass through the intestinal
16 barrier including passage of BoNT complexes containing hemagglutinins (HAs) via M cells,
17 HA-dependent perturbation of E-cadherin intercellular junctions between enterocytes and
18 paracellular passage of BoNT complexes, and transcytosis of BoNT free of NAPs through
19 certain intestinal epithelial cells. Then, BoNTs target neuronal cells, preferentially cholinergic
20 neurons, in the intestinal mucosa and submucosa. The precise mode of BoNT dissemination
21 until the final target neuro-muscular junctions is still elusive.
22

23 **Key Words:** Botulinum neurotoxin, intestinal barrier, M cell, transcytosis, E-cadherin,
24 Cdc42, acetylcholine.
25

26 **1 – Introduction**

27 Botulinum neurotoxins (BoNTs) are the most potent poisonous substances responsible
28 for flaccid paralysis (botulism) which is often lethal in the absence of appropriate treatment.
29 Naturally acquired botulism mainly results from ingestion of preformed BoNT in
30 contaminated food (foodborne botulism) or from an intestinal colonization by *Clostridium*
31 *botulinum* and toxin production *in situ* (infant botulism and more rarely adult intestinal
32 botulism) (Sobel, 2005). The first and critical step of these two forms of botulism consists of
33 BoNT crossing through the intestinal epithelial barrier and dissemination to the target

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