Central mechanism of botulinum toxin action on pain supersensitivity, allodynia and migraine

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Experimental and clinical observations suggest beneficial effect of botulinum toxin A (BoNT/A) in different painful conditions. It was assumed that antinociceptive action is associated with BoNT/A enzymatic inactivation of SNAP25 and prevention of neurotransmitter release from the peripheral nerve endings. However BoNT/-A is more potent and faster acting if applied intrathecally, in some experimental condition injected unilaterally acts bilaterally, and its action can be prevented by axonal transport blocker colchicine. Tracing toxin enzymatic activity we found immunohistochemically that it is transported to sensory regions of the CNS. All these observation suggest central action of BoNT/A (review Matak and Lackovic, Prog Neurobiol 2014). However, molecular mechanism is still unknown. Application of receptor blocking drugs revealed association with opioid and GABA system. Because BoNT/A is registered for treatment of chronic migraine recently we concentrated more on its action in trigeminal region. Surprisingly, three different types of pain: infraorbital nerve constriction injury, temporomandibular joint inflammation and facial formalin injection in rats are accompanied by dural neurogenic inflammation characterized by extravasation of plasma proteins and inflammatory cells. Such phenomenon was previously described only in association with migraine. Immunohistochemistry revealed cocalization of BoNT/A enzymatic activity with calcitonin gene related polypeptide (CGRP) in dural nerves, and biochemically we found increase in dural CGRP level. Thus it seems that after peripheral injection BoNT/A is taken up by sensory nerve endings and axonally transported to dural nerves where it is colocalized with CGRP and suppress its action on neurogenic inflammation (Lackovic et al 2016). This previously unknown phenomenon is specific only for trigeminal region, since peripheral types of pain like partial transection of the sciatic nerve and sciatic nerve constriction injury are not associated with extravasation of lumbar or cranial dura.

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