J Physiol 591.4 (2013) p 749

PERSPECTIVES

Direct central action of intramuscularly injected botulinum toxin: is it harmful or beneficial?

Ryuji Kaji
Professor and Chairman, Department of Neurology, Institute of Health-Bioscience, Tokushima University, 2-50-1 Kuramoto-cho, Tokushima 770-8503, Japan

Email: rkaji@clin.med.tokushima-u.ac.jp or kajkyoto@mbox.kyoto-inet.or.jp

Botulinum toxin has been clinically used for a variety of conditions ranging from cosmetic applications to post-stroke spasticity. Its potential central *versus* peripheral site of action has been a matter of debate, particularly as regards health and safety for the more indiscrimate cosmetic uses (Caleo & Schiavo 2009). Several animal studies indicated its direct central action after central (Akaike *et al.* 2013) or peripheral application of the toxin (Caleo & Schiavo, 2009). It is now becoming clear that some of its clinical benefits cannot be explained without assuming direct central effects (Filipovic *et al.* 2012). Most of the pain-relieving effects of the peripherally applied toxin have been interpreted as suppressing central sensitization. Its central action is plausible because botulinum toxin shares biological characteristics with tetanus toxin, which is widely recognized to have mainly central actions after peripheral application.

In this issue of *The Journal of Physiology*, Marchant-Pauvert *et al.* (2013) provided physiological evidence that the toxin has direct central actions after intramuscular injection in post-stroke patients. They investigated the spinal recurrent Renshaw inhibition, which is known to be di-synaptic and would not have been affected by the injection without assuming a retrograde central effect.

This paper has dual significance. First, it convincingly showed the first evidence of the direct central action in humans using a physiological technique. Secondly, their findings have an important clinical implication in treating stroke patients with botulinum neurotoxin A (BoNT-A), because of the importance of the premotor circuit involved (Renshaw cell) and because of the possibility of locally modulating the pattern of its connections.

Recent clinical trials have witnessed drastic regaining of the active function of the limbs in some patients using a functional outcome measure (disability rating scale) (Marchand-Pauvert *et al.* 2013). In this issue of *The Journal of Physiology*, Marchand-Pauvert *et al.* (2013) show that the muscle paralysing agent BoNT-A increased the grasp power after injections into finger flexors followed by intensive rehabilitation of the treated limbs. This paradox, which has not been explained before, is now better understood by assuming a direct central action of BoNT-A, as revealed in their study.

Spasticity is a syndrome of motor dysfunction caused by loss of upper motor neurons and maladaptive plasticity, involving massive synaptic reorganization at the spinal cord level. This may increase the deep tendon reflexes in late stages after stroke. Intensive rehabilitation after stroke has been the mainstay in treating the motor deficit, possibly enhancing the efficacy of indirect descending pathways from the unaffected cortices including the premotor area. However, the beneficial effect of rehabilitation is known to plateau around 6 months after stroke. One interpretation of this limitation is that abnormal spinal plasticity makes it impossible for the newly developed descending pathway to gain access to the lower motor neuron pools. It is plausible that direct spinal action of BoNT-A results not only in motor terminal degeneration but also in central synaptic reorganization after retrograde transport, so that the supraspinal descending pathways may re-establish contacts with lower motor neurons and their vicinity.

Although this view needs to be tested in further animal and clinical studies, the technique of intramuscular BoNT-A injection followed by intensive rehabilitation may bring about a clinical means of central synaptic modification and a solution to the major healthcare burden to stroke survivors. Thus far, no serious adverse events have been reported in spasticity treatment with BoNT-A, despite its presumed direct central action.

References

Akaike N, Shin MC, Wakita M, Torii Y, Harakawa T, Ginnaga A, Kato K, Kaji R & Kozaki S (2013). Transynaptic inhibition of spinal transmission by A2 botulinum toxin. *J Physiol* **591**, 1031–1043.

Caleo M & Schiavo G (2009). Central effects of tetanus and botulinum neurotoxins. *Toxicon* **54**, 593–599.

Filipovic B, Matak I, Bach-Rojecky L & Lackovic Z (2012). Central action of peripherally applied botulinum toxin type A on pain and dural protein extravasation in rat model of trigeminal neuropathy. *PLoS One* **7**, e29803.

Kaji R, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M, GSK1358820 Spasticity Study Group (2010). Botulinum toxin type A in post-stroke upper limb spasticity. *Curr Med Res Opin* **26**, 1983–1992.

Marchand-Pauvert V, Aymard C, Giboin LS, Dominici F, Rossi A & Mazzocchio R (2013). Beyond muscular effects: depression of spinal recurrent inhibition after botulinum neurotoxin A. *J Physiol* **591**, 1017–1029

DOI: 10.1113/jphysiol.2012.246322