Focal hand dystonia – a disorder of neuroplasticity?

The term dystonia collectively refers to a heterogeneous group of movement disorders characterized by sustained involuntary muscle contractions that result from co-contracting antagonistic muscles and overflow into extraneous muscles (Hallett, 1998). Like other types of focal dystonias, writer’s cramp develops in the absence of known structural changes in the nervous system and it often requires extensive repetition of movements to emerge. The pathophysiology of dystonia has been shown to comprise abnormalities in both motor and somatosensory systems.

Neuronal representations are believed to be shaped by prior experience through physiological processes commonly referred to as neuroplasticity. Numerous studies have revealed that neuronal representations may be altered in focal hand dystonia. One such alteration is a severe degradation of finger representations in the somatosensory cortex which are normally highly somatotopically organized (Bara-Jimenez et al., 1996). Although considerable disagreement exists as to whether such abnormalities of somatosensory processing alone are sufficient to induce a dystonic phenotype, two other questions are raised by these observations. First, do the abnormal movements in dystonia themselves lead to somatosensory disorganization and second and/or is there a fundamental deficit in the physiological mechanisms underlying neuroplasticity in patients with focal dystonias?

In this issue of Brain, Quartarone et al. (2003) take an important step toward answering the second question. The authors used a timed interaction between events induced by afferent electric nerve and transcranial magnetic stimulation in the motor cortex (termed paired associative stimulation, PAS) to induce lasting changes of excitability of the corticospinal system of patients with writer’s cramp. Based on the model’s physiological properties, PAS-induced cortical excitability changes have been proposed to represent a model of long-term potentiation (LTP) of synaptic efficacy (Stefan et al., 2000; Wolters et al., 2003), which is probably one of the principal cellular mechanisms of neuroplasticity in the brain. PAS-induced cortical excitability changes are characterised by rapid evolution, persistence, dependence on N-methyl-D-aspartate receptor activation, and topographical specificity (Stefan et al., 2000). Further, in support of a synaptic nature of PAS-induced physiological effects, the sign of excitability changes is determined by the exact sequence of near-synchronous motor cortical events evoked by the two stimulation modalities (Wolters et al., 2003), similar to the spike-timing dependent plasticity rule governing the modulation of synaptic efficacy by associative (or ‘Hebbian’) stimulation. While the significance of this model for normal behaviour is unknown, recent data suggest that it may be linked to motor learning in a manner similar to motor cortical LTP (Wycislo and Classen, 2003).

When Quartarone’s patients were exposed to repetitive right median nerve stimulation paired with transcranial magnetic stimulation over the homologous motor representation in left primary motor cortex, the size of the motor evoked potential elicited by transcranial magnetic stimulation in the right abductor pollicis muscle increased. The magnitude of the increase substantially exceeded that in healthy controls. Furthermore, the patients also exhibited an increase in the amplitude of the motor evoked potential recorded from the first dorsal interosseous muscle. This differed from the situation in the controls, where the cortical excitability increase was largely restricted to the muscle representation, whose central representation was conjointly stimulated by the two stimulation modalities. Thus, the brain’s response to PAS was exaggerated and its spatial specificity was reduced in writer’s cramp.

This finding is noteworthy because it provides the most direct evidence to date that a fundamental mechanism underlying neuronal plasticity is abnormal in focal dystonia. Importantly, the present results suggest that derangement of motor representations may arise even in the presence of an orderly pattern of peripheral input, obviating the need for unphysiological stimulus configurations in previous patho-genetic models.

A large number of neurophysiological studies have revealed decreased neuronal inhibition in focal dystonia at multiple levels of the central motor system including the primary motor cortex. Neuronal disinhibition promotes LTP in animal studies and also may facilitate PAS-induced excitability changes in humans. Furthermore, pre-existing
dedifferentiation of somatosensory representations in dystonia may not provide a sufficiently focused cortical input for allowing spatially well defined motor memories to arise. These considerations suggest that the abnormalities of neuronal plasticity in writer’s cramp may well be a direct consequence of previously known physiological abnormalities. On this view, the new findings are particularly interesting as they provide a pathophysiological model of focal hand dystonia linking somatosensory with motor system abnormalities.

Neuronal inhibition, however, is subject to plastic changes, just as synapses are that mediate excitatory neurotransmission. Quartarone and co-workers show that writer’s cramp patients lack the normal PAS-induced prolongation of the silent period, a physiological measure likely related to neuronal inhibition mediated by GABAB-receptors. Therefore, the present results leave room for the alternative hypothesis that disturbance of LTP-like mechanisms may represent an early pathogenetic abnormality in focal dystonia with only later consequences on neuronal inhibition and representational differentiation. Irrespective of the precise position in the sequence of pathogenetically relevant events in dystonia, the findings by Quartarone and co-workers seem to imply that all known physiological abnormalities mutually re-enforce each other with the effect of stabilizing pathological movement representations.

Therapeutic approaches involving the practice of movements are likely to remain unsuccessful unless their design includes a framework that, in principle, aims at interrupting this vicious circle. Indeed, a recently developed behavioural therapy, termed sensory motor retuning, holds great promise (Candia et al., 2002). Musicians with focal hand dystonia performed repetitive movements with fingers of their dystonic hand while one or more fingers except the dystonic ones were immobilized. After therapy, movements of the dystonic fingers were substantially better controlled, with some musicians reaching near-normal performance levels. Along with improvement of motor behaviour, the topography of the somatosensory representation of the fingers became normalized (Candia et al., 2003). Another group has focused on reinstalling the orderly topography of the somatosensory maps, with fairly good results on motor performance (Zeuner et al., 2002). Now, that we have strong direct evidence of abnormal neuroplasticity mechanisms in focal dystonia, we can even imagine applying external associative stimulation protocols tailored to reverting physiological abnormalities as an adjunct to behavioural therapy of this disabling disorder.

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Acknowledgements

I would like to thank Professors M. Naumann and K.V. Toyka for helpful comments.

References


