Pathophysiology of writer's cramp

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Abstract

Writer's cramp is a task-specific focal hand dystonia. The abnormality of task specificity is a curious one and indicates that we need to learn more about the coupling of motor programs and their effectors. Writer's cramp appears to be triggered by spending much time writing by an individual with a fertile physiological substrate for producing the disorder. The fertile background, which is likely genetic, may be a decrease of inhibition, an increase of plasticity or an impairment in sensory function. Recent pathophysiological findings have implications for new therapies.
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1. Introduction

The term writer's cramp, by analogy to common muscle cramps, is often used loosely to describe a pain in the hand after writing for a long time. At least for neurologists, the term refers to a task-specific, focal hand dystonia. Dystonia is the term for a set of disorders characterized by abnormal postures and unwanted muscle spasms that interfere with motor performance (Hallett, 2004). Focal dystonias are the most common and refer to dystonia of just one body part. Focal hand dystonias are relatively common, but less frequent than focal dystonias of the neck (cervical dystonia) or eyelids (blepharospasm). Task specificity is a fascinating aspect of writer's cramp; it means that only writing is abnormal, other tasks are normal. Writer's cramp is not the only task-specific focal hand dystonia; almost

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any task can be affected. Other frequent task-specific hand dystonias are typist's cramp and musician's cramp, including pianist cramp and flautist cramp. At times, when the disorder gets worse the task specificity is lost, and the dystonia can affect other tasks and even become spontaneous. The task specificity is clinically apparent, but with careful assessment a more pervasive, if mild, motor control disorder can be demonstrated. This point will be discussed later in the physiological studies.

Writer's cramp is generally seen in persons who have spent much time writing. A long period of stereotyped, repetitive behavior seems to be important. Clearly all persons who do considerable writing do not develop writer's cramp. Hence, the most likely scenario is that, like most diseases, writer's cramp is a product of a genetic background and an environmental insult. That is, writer's cramp develops with excessive writing only in those persons who are genetically predisposed. And, indeed, there is evidence that there is a genetic influence in the focal dystonias (Defazio et al., 2003; Defazio, Brancati et al., 2003). There is an increase in the family incidence of the focal dystonias that suggests that all the focal dystonias are related to each other and that the genetic influence is autosomal dominant with a markedly reduced penetrance.

Work is ongoing trying to identify abnormal genes in patients with focal dystonia, but this is very difficult given the low penetrance. Currently there are some leads. There has been a considerable amount of work trying to understand the pathophysiology of focal dystonia on an integrative level. The abnormalities identified can be of two types: one, a reflection of the genetic abnormality indicating the substrate on which the dystonia develops, and two, a reflection of the developed dystonia on the background substrate. As noted before, presumably, the environmental trigger is the repetitive movement. Because of the relative ease of studying the hand compared with other body parts, many of the studies of the pathophysiology of focal dystonia have been done with focal hand dystonia, and writer's cramp in particular.

2. Task specificity

It is worth contemplating the curious nature of a task-specific disorder. The effector, in this case the hand, is normal (or close to normal) for all tasks except one. So the basic movement control mechanisms must be functioning reasonably well. Also, the motor program for the task must be all right since other effectors can carry out the motor program. For writer's cramp, for example, writing is likely normal for the other hand and even for the affected limb if the writing is done with more proximal muscles, such as writing on a blackboard. Hence, the essence of the problem is the specific linkage of the one motor program to one effector. The nexus for this linkage is not known.

There have been a large number of neuroimaging studies of various types of hand movements. Common in virtually all of them is activation of the contralateral primary motor cortex, the contralateral primary sensory cortex, the premotor cortex and the supplementary motor area bilaterally, and the cerebellum ipsilaterally (Hanakawa et al., 2003; Hanakawa, Parikh, Bruno, & Hallett, 2005). One study has been conducted looking to define the common network for handwriting (Rijntjes et al., 1999). This was done by comparing writing with zigzag movements of both hand and foot. The regions identified were the anterior part of the dorsal part of the premotor cortex (PMd), the ventral part of the premotor cortex (PMv), the supplementary motor area (SMA), area MIP and VIP in the intraparietal sulcus, the thalamus, the cerebellar hemispheres, posterior part of the superior

parietal cortex, probably corresponding to Brodmann area 7, and the occipitotemporal junction, thought to be the visual motion center (V5/MT). The parts of the PMv and PMd that were common were those activated by the hand when making zigzag movements. The authors concluded that their results showed that movement parameters for this writing are stored in secondary sensorimotor cortices of the extremity with which it is usually performed, that is, the dominant hand, including dorsal and ventral lateral premotor cortices. This study does indicate that there are a large number of possible overlap areas between program and effector.

Task specificity has been seen physiologically with studies of the contingent negative variation (CNV) (Kaji et al., 1995). The CNV is a slow negative EEG potential that arises between two stimuli triggering a reaction time movement. The first stimulus, S1, acts as a warning stimulus, and after an interval, the second stimulus, S2, "commands" the movement. The beginning of the CNV is thought to be related to sensory processing of S1 and the end of the CNV is thought to be related to motor preparation. The terminal part of the CNV is defective for neck turning in patients with cervical dystonia, while it is normal for hand movements (Kaji et al., 1995). Conversely, the terminal part of the CNV is defective for hand movements in patients with writer's cramp, while it is normal for neck turning (Hamano et al., 1999). Many cortical areas appear to participate in the CNV so it is not certain what areas may be malfunctioning (Hamano et al., 1997).

There have been many neuroimaging studies of hand movement tasks in patients with focal hand dystonia. The results are not uniform, likely due to the differences in patients and the nature of the task performed. In relation to the discussion here, the positron emission tomography (PET) study of Ibanez, Sadato, Karp, Deiber, and Hallett (1999) may be valuable to consider. This study looked at cerebral blood flow in patients with writer's cramp during various movement tasks including writing. During handwriting there was deficient activation in the premotor cortex in the patients compared with normal control participants. As the premotor cortex is one of the prominent areas for overlap between program and effector, this might be a critical area for problems in patients.

3. Pathophysiological findings in focal dystonias

There are three general lines of work at the present time that may indicate the physiological substrate for dystonia. All three are persuasive and it is not clear whether they are related to each other or whether one is more fundamental than the others.

3.1. Loss of inhibition

A principal finding in focal dystonia is that of loss of inhibition (Hallett, 2004). Loss of inhibition is likely responsible for the excessive movement seen in dystonia patients. Excessive movement includes abnormally long bursts of EMG activity, co-contraction of antagonist muscles, and overflow of activity into muscles not intended for the task (Cohen & Hallett, 1988). Loss of inhibition can be demonstrated in spinal and brainstem reflexes. Examples are the loss of reciprocal inhibition in the arm in patients with focal hand dystonia (Nakashima et al., 1989; Panizza, Lelli, Nilsson, & Hallett, 1990) and abnormalities of blink reflex recovery in blepharospasm (Berardelli, Rothwell, Day, & Marsden, 1985). Loss of reciprocal inhibition can be partly responsible for presence of co-contraction of antagonist muscles that characterizes voluntary movement in dystonia.

Loss of inhibition can also be demonstrated for motor cortical function including short intracortical inhibition, long intracortical inhibition, and the silent period.

Short intracortical inhibition (SICI) is obtained with paired pulse methods and reflects interneuron influences in the cortex (Ziemann, Rothwell, & Ridding, 1996). In such studies, an initial conditioning stimulus is given, enough to activate cortical neurons, but small enough that no descending influence on the spinal cord can be detected. A second test stimulus, at suprathreshold level, follows at short interval. Intracortical influences initiated by the conditioning stimulus modulate the amplitude of the motor evoked potential (MEP) produced by the test stimulus. At short intervals, less than 5 ms, there is inhibition that is likely largely a GABAergic effect, specifically GABA-A (Di Lazzaro et al., 2000). (At intervals between 8 and 30 ms, there is facilitation, called intracortical facilitation, ICF). There is a loss of intracortical inhibition in patients with focal hand dystonia (Ridding, Sheean, Rothwell, Inzelberg, & Kujirai, 1995). Inhibition was less in both hemispheres of patients with focal hand dystonia, and this indicates that this abnormality is more consistent as a substrate for dystonia.

The silent period (SP) is a pause in ongoing voluntary EMG activity produced by TMS. While the first part of the SP is due in part to spinal cord refractoriness, the latter part is entirely due to cortical inhibition (Fuhr, Agostino, & Hallett, 1991). This type of inhibition is likely mediated by GABA-B receptors (Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999). SICI and the SP show different modulation in different circumstances and clearly reflect different aspects of cortical inhibition. The SP is shortened in focal dystonia.

Intracortical inhibition can also be assessed with paired suprathreshold TMS pulses at intervals from 50 to 200 ms (Valls-Solé, Pascual-Leone, Wassermann, & Hallett, 1992). This is called long intracortical inhibition, or LICI, to differentiate it from SICI as noted above. LICI and SICI differ as demonstrated by the facts that with increasing test pulse strength, LICI decreases but SICI tends to increase, and that there is no correlation between the degree of SICI and LICI in different individuals (Sanger, Garg, & Chen, 2001). The mechanisms of LICI and the SP may be similar in that both seem to depend on GABA-B receptors. Chen, Wassermann, Caños, and Hallett (1997) investigated long intracortical inhibition in patients with writer's cramp and found a deficiency only in the symptomatic hand and only with background contraction. This abnormality is particularly interesting since it is restricted to the symptomatic setting, and therefore might be a correlate of the development of the dystonia.

There is a valuable animal model for blepharospasm that supports the idea of a combination of genetics and environment, and, specifically, that the background for the development of dystonia could be a loss of inhibition (Schicatano, Basso, & Evinger, 1997). In this model, rats were lesioned to cause a depletion of dopamine; this reduces inhibition. Then the orbicularis oculi muscle was weakened. This causes an increase in the blink reflex drive in order to produce an adequate blink. Together, but not separately, these two interventions produced spasms of eyelid closure, similar to blepharospasm. Shortly after the animal model was presented, several patients with blepharospasm after a Bell's palsy was reported (Baker et al., 1997; Chuke, Baker, & Porter, 1996). This could be a human analog of the animal experiments. The idea is that those patients who developed blepharospasm were in some way predisposed. A gold weight implanted into the weak lid of one patient, aiding lid closure, improved the condition suggesting that when the abnormal increase in reflex drive was removed, the dystonia could be ameliorated (Chuke et al., 1996).

A principle for function of the motor system may be "surround inhibition". Surround inhibition is a concept well accepted in sensory physiology (Angelucci, Levitt, & Lund, 2002). Surround inhibition is not so well known in the motor system, but it is a logical concept. When making a movement, the brain must activate the motor system. It is possible that the brain just activates the specific movement. On the other hand, it is more likely that the one specific movement is generated, and, simultaneously, other possible movements are suppressed. The suppression of unwanted movements would be surround inhibition, and this should produce a more precise movement, just as surround inhibition in sensory systems produces more precise perceptions. For dystonia, a failure of 'surround inhibition' may be particularly important since overflow movement is often seen and is a principal abnormality.

There is now good evidence for surround inhibition in human movement. Sohn, Jung, Kaelin-Lang, and Hallett (2003) have shown that with movement of one finger there is widespread inhibition of muscles in the contralateral limb. Significant suppression of MEP amplitudes was observed when TMS was applied between 35 and 70 ms after EMG onset. Sohn et al. have also shown that there is some inhibition of muscles in the ipsilateral limb when those muscles are not involved in any way in the movement (Sohn & Hallett, 2004b). TMS was delivered to the left motor cortex from 3 to 1000 ms after EMG onset in the flexor digitorum superficialis muscle. MEPs from abductor digiti minimi were slightly suppressed during the movement of the index finger in the face of increased F-wave amplitude and persistence, indicating that cortical excitability is reduced.

Surround inhibition was studied similarly in patients with focal hand dystonia (Sohn & Hallett, 2004a). The MEPs were enhanced similarly in the flexor digitorum superficialis and abductor digiti minimi indicating a failure of surround inhibition. Using another experimental paradigm, Stinear and Byblow have also found a loss of surround inhibition in the hand (Stinear & Byblow, 2004).

3.2. Abnormal plasticity

There is an abnormal plasticity of the motor cortex in patients with focal hand dystonia (Quartarone et al., 2003). This has been demonstrated using the technique of paired associative stimulation (PAS) (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). In PAS, a median nerve shock is paired with a TMS pulse to the sensorimotor cortex timed to be immediately after the arrival of the sensory volley. This intervention increases the amplitude of the MEP produced by TMS to the motor cortex. It has been demonstrated that the process of PAS produces motor learning similar to long-term potentiation (LTP). In patients with dystonia, PAS produces a larger increase in the MEP than what is seen in normal participants.

Another aspect of the abnormal plasticity has recently been identified. Not only is the plasticity increased, but there is a failure of its homeostatic property (Quartarone et al., 2005). The homeostatic property is that plasticity ordinarily increases and decreases within bounds. If, for example, the excitability of the motor cortex is high, then it cannot be driven higher, only lower. The recent finding, using several types of brain stimulation, is that plasticity in dystonia may not be properly bounded and may increase abnormally.

Increased plasticity may arise from decreased inhibition so the inhibitory problem may well be more fundamental. This abnormality may be an important link in demonstrating how environmental influences can trigger dystonia.

The possibility of increased plasticity in dystonia had been suspected for some time given that repetitive activity over long periods seems to be a trigger for its development. An

animal model supported this idea (Byl, Merzenich, & Jenkins, 1996). Monkeys were trained to hold a vibrating manipulandum for long periods. After some time, they became unable to do so, and this motor control abnormality was interpreted as a possible dystonia. The sensory cortex of these animals was studied, and sensory receptive fields were found to be large. The interpretation of these results was that the synchronous sensory input caused the receptive field enlargement, and that the abnormal sensory function led to abnormal motor function. The results suggested that the same thing might be happening in human focal dystonia; repetitive activity caused sensory receptive field changes and led to the motor disorder.

3.3. Abnormal sensory function

Stimulated by the findings of sensory dysfunction in the primate model, investigators began examining sensory function in patients with focal hand dystonia and found it to be abnormal. Although there is no apparent sensory loss on a clinical level, detailed testing of spatial and temporal discrimination revealed subtle impairments (Molloy, Carr, Zeuner, Dambrosia, & Hallett, 2003). The abnormality is present on both hands of patients with unilateral hand dystonia and also on hands of patients with cervical dystonia and blepharospasm. The identification of abnormality of sensation beyond the symptomatic body parts indicated that the sensory abnormality could not be a consequence of abnormal learning, but is more likely a pre-existing physiological state.

Sensory dysfunction can also be demonstrated with somatosensory evoked potential (SEP) testing (Bara-Jimenez, Catalan, Hallett, & Gerloff, 1998). The dipoles of the N20 from stimulation of individual fingers show disordered representation in the primary sensory cortex (Bara-Jimenez et al., 1998) and these abnormalities are present on both hands of patients with focal hand dystonia (Meunier et al., 2001). The bilateral SEP abnormality was the first indication in the literature that the sensory abnormality was more likely endophenotypic than a consequence of repetitive activity. PET studies show that the sensory cortex is more activated than normal with writing and is more activated when patients are experiencing more dystonia (Lerner et al., 2004). Voxel-based morphometry studies in patients with focal hand dystonia show an increase in gray matter in the primary sensory cortex (Garraux et al., 2004). Such observations indicate that dystonia is a sensory disorder as well as a motor disorder.

4. Therapeutic implications

There are therapeutic implications of this pathophysiological information. Since inhibition is deficient, it is logical that increase of inhibition should be beneficial. It has been known empirically that medications like clonazepam and baclofen can be helpful, and now we understand why this should be so. Slow rates of repetitive TMS (1 Hz) to the primary motor cortex, that increase cortical inhibition, can be helpful (Siebner et al., 1999). Benefit has also been seen with 0.2 Hz stimulation of the premotor cortex (Murase et al., 2005).

If plasticity is increased, then it should be able to be exploited to return a person to normal as well as to produce the dystonia in the first place. This concept has given rise to the idea that motor training might be helpful (Candia et al., 2002). In the method called sensorimotor retuning, individual fingers are trained with playing keys on a piano while the other fingers were splinted. Significant success has been seen, rather rapidly, in some piano players, but there was no effect with musicians who play wind instruments. With a similar

method designed for patients with writer's cramp, individual fingers practice writing with finger pens while the other fingers are splinted (Zeuner et al., 2005). Again, some improvement in the dystonia was found. Another technique that might utilize mechanisms of plasticity is immobilization (Pesenti, Barbieri, & Priori, 2004; Priori, Pesenti, Cappellari, Scarlato, & Barbieri, 2001). The arm and hand are immobilized in a cast for about 4 weeks; after the arm comes out of the cast, it is slowly "re-trained" to move again. To the extent that this works, it might be due to a dedifferentiation of the sensorimotor cortex during the immobilization and an eradication of the abnormal dystonic patterns.

There is an interesting therapeutic implication also from the abnormal sensory function. If sensory function can be normalized, perhaps motor function would be improved. The possibility of this working seems increased given the abnormal exaggeration of plastic changes. We have shown that sensory training can lead to improved sensory discrimination and improved motor function (Zeuner et al., 2002; Zeuner & Hallett, 2003). Sensory training was accomplished by training each individual finger to read Braille.

Another therapeutic approach arising from the idea of sensory dysfunction is muscle afferent block (Kaji et al., 1995). Injection of dilute lidocaine into muscle preferentially blocks the gamma efferents causing a decrease in spindle afferent discharge. This maneuver improves focal hand dystonia transiently.

With regard to therapy, focal injection of botulinum toxin should not be overlooked. It is still likely the most effective form of therapy even though it is clearly far from curative. Botulinum toxin works to some extent certainly by weakening the specific muscles that spasm, but there is some evidence for a central nervous system effect as well. Any central nervous system effect is likely due to a central reaction to the peripheral effect of the toxin, most likely the reduction in spindle discharge because of the denervation of the muscle spindle (Hallett, 2000).

For all of the rehabilitative type therapies, it is reasonable to ask how long the benefit will last. Most studies have been short term and there is no report of lasting benefit. In the sensory training studies, participants were followed after they stopped training and both the improvement in sensory discrimination and motor performance reverted to the baseline abnormal state (Zeuner et al., 2002). If there is abnormal homeostatic plasticity, there would be a drive to the abnormal state again. On the other hand, since it takes many years to develop the disorder, it may require many years of rehabilitation to lead to a more permanent improvement.

5. Conclusion

Writer's cramp is a fascinating condition. Studies of its pathophysiology not only are important for understanding all focal dystonias, but also for illuminating principles of human motor control. Recent findings have been useful in suggesting new therapeutic approaches to the disorder.

6. Ethical declaration

All experimental work involving human participants done in the author's laboratory has been carried out according to the ethical guidelines laid down by the NIH Institutional Review Board.

Acknowledgement

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