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CORTICAL PLASTICITY AND ITS IMPLICATIONS FOR FOCAL HAND DYSTONIA

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Background: The exact origin of focal dystonias has not been elucidated so far. Aberrant plasticity of the brain cortex is suspected to be a crucial factor in the development of this group of movement disorders. The aim of this article is to summarize recent findings on the etiopathogenesis of focal hand dystonias with a focus on the role of abnormal cortical plasticity.

Methods And Results: A search of the literature mainly from 1995 to 2005 was done using the PubMed and Ovid search engines. English-language articles were identified using the following keywords: focal hand dystonia or writer's cramp and cortical plasticity, sensorimotor, imaging. Additional references were found through bibliography reviews of relevant articles. The data from neurophysiological and imaging studies, as well as clinical observation, in focal hand dystonia suggest multiple failures at different levels of the somatosensory and motor systems, particularly in the brain cortex. This disorders lead to attenuation of inhibitory and fortification of excitatory processes.

Conclusions: The emerging theory presumes that a maladaptive plasticity of brain cortex with abnormal sensorimotor intergration can evolve in predisposed individuals. Consequent methods of management of focal hand dystonias are outlined.

INTRODUCTION

Over the past several decades, there has been enormous progress in our understanding of the structure and function of the cerebral cortex. One of the most significant discoveries is the knowledge that the adult mammalian brain cortex is not a rigid structure, but is dynamically reorganized throughout life by experience, learning and central or peripheral insults. This phenomenon is known as cortical plasticity[1].

The pioneer of the term cortical plasticity at the beginning of the 20th century was the Italian psychiatrist Ernesto Lugano. Basic studies in the field were initiated by Donald Hebb, who showed that in rats neuronal cortical synapses are strengthened and remodeled by experience[2].

Cortical plasticity can be subdivided into two types: adaptive and maladaptive. Adaptive plasticity results in the enhancement of special skills with practice and learning. It allows the brain to compensate for lost functionality due to brain injury of various etiologies (e.g. stroke), damaged motor efferentation (e.g. peripheral nerve lesions) or changes in sensory input (amputation, local anaesthesia). In contrast, excessive plasticity leading to neurological diseases such as mesial temporal sclerosis or focal hand dystonia is maladaptive[3].

Several mechanisms have been implicated to underlie plasticity of the nervous system at the cellular level: growth of new neurons (neurogenesis), axonal sprouting with new synapse formation, unmasking or potentiation of existing but normally ineffective neural connections. Whereas the first mentioned mechanism represents in an adult mammalian brain a rather debated exception limited to the hippocampal dentate gyrus and olfactory bulb[4], de-novo growth of axonal branches and synapses have been described several weeks after lesioning CNS afferents[5] and modification of existing synapses takes place within several minute after the insult[6]. In the following text, we will first discuss the last mentioned mechanism, modification of existing synapses, which seems to dominate the adult mammalian CNS.

The basic processes of synaptic plasticity in the mammalian central nervous system are known as long-term potentiation (LTP) and long-term depression (LTD). LTP is defined as a long-term enhancement of synaptic strength resulting from repeated activation of synapses. LTD refers to the opposite phenomenon, a decline in synaptic strength. These processes are highly complicated and not fully elucidated to date - the majority of cellular structures take part in them. A crucial role in the regulation of LTP involves the activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and especially N-methyl-D-aspartate (NMDA) type of glutamate receptor followed by Ca^{2+} ion entry into post-synaptic neurons[3]. Depending on the duration, strength, and site of Ca^{2+} action, phosphatase calcineurin modulates ion channels, neurotransmitter receptors, cytoskeletal proteins, transcription factors and neurotrophins. In this way, calcineurin initiates both short- and long-term changes in neuronal activity leading to modification of neural plasticity[7]. Compared to the effects exhibited by the NMDA receptor, the gamma-aminobutyric acid (GABA)

receptor exhibits the opposite phenomenon. Nitric oxide (NO) also plays a role in these processes[8].

Dendritic spines are considered to be a key structure in neuronal plasticity. They are covered with a large number of excitatory receptors, particularly glutamate NMDA receptors. Numerous electron-microscopy studies have shown the ability of the spines to change number and shape dynamically after exogenous stimulation[9].

Components of the spines play distinct roles in processes of plasticity. The volume of the spine head is important for the regulation of synaptic transmission, possibly through variation of functional glutamate receptor expression. By contrast, the spine neck can, within minutes, influence synaptic signaling through the control of Ca^{2+} influx into dendrites and in this way directly control communication between the spine and dendrite. As a result, this structure is considered to play a decisive role in the induction of synaptic plasticity[10].

Synaptic plasticity of the LTP-type was first described in the hippocampus[11] but under specific experimental conditions has also been observed in the neocortex[12].

Another important mechanism involved in brain plasticity is neurogenesis. Its significance is highest in the postnatal period, but recently it was demonstrated in the adult human brain, too. The source of neurogenesis is allegedly neural stem cells located especially in the hippocampus and in the subventricular zone. However, the existence of neurogenesis outside of a limited area of archicortex remains disputed[4].

There is increasing evidence that glial cells, in particular astrocytes, also play an essential role in brain plasticity. This is accomplished through the regulation of the synaptic environment and maintenance of appropriate levels of neurotransmitters and neurotrophins[14].

Focal hand dystonia

As mentioned above, focal hand dystonias are a significant example of disease with presumed involvement of maladaptive cortical plasticity in their pathogenesis. Dystonia is a disorder characterized by persistent involuntary muscle contractions causing sustained twisting movements and abnormal postures of the affected body parts. Excessive co-contractions of agonist and antagonist muscles, difficulty in activating the appropriate muscles and overflow of muscular activity into extraneous muscles can all occur in dystonia. Focal hand dystonias include writer's cramp, typist's cramp, pianist's cramp and others. These occupational, disabling diseases are usually triggered by the long-term repetition of quickly alternating, highly skilled movements. Therefore these types of dystonias are known as task-specific.

The exact pathophysiology of dystonias is unknown, though it is widely held that dysfunction of the corticostriatal-thalamocortical motor circuits plays a major role[3, 15]. A fundamental finding in the field of cortical plasticity in focal hand dystonias came from primates. Monkeys performed a repetitive digital grasp task while weak vibratory stimuli were delivered to the hand. After several weeks of repetitive practice, their motor performance deteriorated. Subsequent examination of the somatosensory cortex revealed an alteration in the cortical representation of the hand with fusion of individual finger boundaries[16]. Similar observations were made in the human models.

Neurophysiological and imaging methods

In the study of cortical plasticity, imaging and neurophysiological methods can be used. Imaging methods differ in temporal and spatial resolution. Positron emission tomography (PET) displays brain activity with a temporal resolution of minutes and spatial resolution of 1 cm^3. Temporal and spatial resolution of functional magnetic resonance imaging (fMRI) is in the order of seconds and cubic millimeters, respectively. Electroencephalography and magnetoencephalography excel with a temporal resolution of milliseconds, but their spatial resolution is lower. One of the most frequently used neurophysiological methods is transcranial magnetic stimulation (TMS). A suitable modification of TMS, known as paired associative stimulation, involves repetitive peripheral nerve stimulation paired with supra-threshold TMS over the homologous primary motor cortex. The increased cortical excitability is expressed as growth of motor evoked potentials (MEP) amplitude. This amplitude probably corresponds to the processes associated with LTP. Among the parameters likely associated with cortical inhibition are cortical silent period (CSP), short-latency intracortical inhibition (SICI), and interstimulus interval (ISI). Different parameters of somatosensory evoked potentials (SEP) serve for the study of analogous processes in the somatosensory system[15, 17].

With the help of PAS, significantly higher excitability of the motor cortex with a decreased specificity of individual finger representations was detected in patients with writer's cramp. The observation of only minimally prolonged CSP in patients compared to healthy volunteers is important evidence of attenuation of intracortical inhibitory processes in motor cortex[17].

Although the primary manifestation of task-specific hand dystonia is a motor abnormity, there is growing evidence showing a role of the disorder in dysfunctions localized to different levels of the somatosensory system. It has been known for a long time that a change of hand posture or tactile and proprioceptive stimulation of specific sites within the affected region (geste antagonistique) can alleviate dystonic symptoms[18]. Patients suffering from dystonia often describe ill-defined feelings of discomfort, pain, and kinaesthetic sensations before the clinical manifestations of the disease[19]. Many neurophysiological studies have demonstrated failures of temporo-spatial somatosensory discrimination[20]. Other studies have confirmed disorders of inhibitory functions at spinal, brain stem, and cortical levels of the somatosensory system, particularly in relation to proprioceptive afferentation[21]. Fusion in the cortical sensory representation of dystonic hand fingers has been observed[22]. Another interesting study has demonstrated abnormal cortical finger representations from the non-dystonic hand[23]. Bilateral alteration of sensory processing has also been found in

asymptomatic first-degree relatives of patients with focal dystonia[24].

Findings from neurophysiological methods are congruous with information obtained from imaging methods. An fMRI study of patients with writer's cramp during writing demonstrated more significant activation of contralateral thalamus, ipsilateral cerebellar hemisphere, and in particular contralateral primary sensorimotor cortex extending to the premotor association area, in comparison with healthy subjects. This finding supports a hypothesis of extensive motor cortex activation via the thalamus in writer's cramp patients[25]. Another fMRI study demonstrated overlapping and even inversion of particular finger representation in the S1 area of task-specific hand dystonia patients[26]. Similar findings were also found in a study using MEG[27]. Significantly decreased levels of GABA in the contralateral sensorimotor cortex and nucleus lenticularis, with insignificant decreases ipsilaterally, have been detected by MR spectroscopy[28]. Voxel-based morphometry study also verified the increased volume of gray matter bilaterally in S1 and decreased volume in M1 areas in patients with writer's cramp[29]. Finally, a study employing PET with $O^{15}H_2O$ has demonstrated increased metabolic activity in the primary somatosensory cortex in patients with focal hand dystonia[30].

Sensorimotor integration

It is generally accepted that the somatosensory system is the main determinant of motor system function. The gamma system comprised of gamma motoneurons, muscle spindles, and their Ia proprioceptive afferentation to the somatosensory cortex, plays this principal role in movement. Every motor performance is a result of interaction between the gamma and alpha system. Any disorder in this interaction results in abnormal movement[31].

Information from the studies mentioned above confirms the hypothesis that fortified excitatory and attenuated inhibitory processes at different levels of the somatosensory system are a characteristic feature for task-specific hand dystonias. Ia afferentation and GABA transmission participate significantly in these disorders. Other components of the motor system that are likely to participate in the pathogenesis of focal dystonias are the basal ganglia and the thalamus. It is likely that the basal ganglia are responsible for the initiation of automatic and highly trained movement routines in relation to sensory inputs. The fundamental structure for interaction between the motor and sensory systems could be the reticular nucleus of the thalamus with an inhibitory effect on somatosensory transmission[15].

In summary, these results suggest that focal hand dystonias develop as a result of disorder in sensorimotor integration. The emerging theory presumes that repetitive sensory stimulation evolving during repetitive skilled movements can, in predisposed individuals, lead to a maladaptive plasticity of the sensorimotor cortex. Consequently, the insufficient inhibition of afferent sensory information results in aberrant movement.

Therapeutic implications

Therapeutic implications for focal dystonias can be extracted from the above hypotheses. Procedures using manipulation of the sensory, particularly proprioceptive, afferentation seem to be promising. One of the effective methods could be immobilization of the affected hand and fingers combined with rehabilitation. This procedure causes a decrease in proprioceptive afferentation as well as motor efferentation, possibly resulting in clinical improvement for the patient. The presumed mechanism is suppression of the maladaptive plasticity with a corresponding decrease in the extent of the excitable motor cortex[32] or decrease of MEP amplitude in TMS[33].

Intramuscular application of botulinum toxin type A into affected muscles is another therapeutic approach. Botulinum toxin blocks neuromuscular transmission in extrafusal muscle fibers as well as intrafusal ones. The afferentation from muscle spindles is subsequently decreased. Neurophysiological studies after the therapy have demonstrated transient normalization of hand cortical motor map following injection[34]. Further studies using neurophysiological methods have verified normalization of inhibitory and excitatory cortical functions in patients with focal dystonia[35].

CONCLUSIONS

The mammalian brain cortex has been continuously modified by the complicated processes of cortical plasticity. But its abnormal increase can lead to pathological conditions such as focal hand dystonia. Although the exact etiopathogenesis of this group of diseases has not been fully elucidated, several findings have already allowed us to alleviate symptoms.

Presumably, future progress in the understanding of processes participating in cortical plasticity will lead to the development of more effective therapy for these and other neurological disorders.

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