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Review

Abnormal plasticity in dystonia: Disruption of synaptic homeostasis

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ABSTRACT

Work over the past two decades lead to substantial changes in our understanding of dystonia, which was, until recently, considered an exclusively sporadic movement disorder. The discovery of several gene mutations responsible for many inherited forms of dystonia has prompted much effort in the generation of transgenic mouse models bearing mutations found in patients. The large majority of these rodent models do not exhibit overt phenotypic abnormalities, or neuronal loss in specific brain areas. Nevertheless, both subtle motor abnormalities and significant alterations of synaptic plasticity have been recorded in mice, suggestive of an altered basal ganglia circuitry. In addition, robust evidence from experimental and clinical work supports the assumption that dystonia may indeed be considered a disorder linked to the disruption of synaptic "scaling", with a prevailing facilitation of synaptic potentiation, together with the loss of synaptic inhibitory processes.

Notably, neurophysiological studies from patients carrying gene mutations as well as from non-manifesting carriers have shown the presence of synaptic plasticity abnormalities, indicating the presence of specific endophenotypic traits in carriers of the gene mutation. In this survey, we review findings from a broad range of data, obtained both from animal models and human research, and propose that the abnormalities of synaptic plasticity described in mice and humans may be considered an endophenotype to dystonia, and a valid and powerful tool to investigate the pathogenic mechanisms underlying this movement disorder. This article is part of a Special Issue entitled "Advances in dystonia".

Contents

Introduction

Dystonia can be defined as a syndrome characterised by prolonged muscle contractions, which cause involuntary repetitive twisting movements and abnormal postures of the affected body parts (Fahn et al., 1998; Müller, 2009).

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It can be focal when the dystonic pattern involve a single body part in isolation or generalized if the abnormal posture affects many segments of the entire body. Some focal dystonias are rather peculiar since symptoms become only apparent if patients perform a specific motor task (Torres-Russotto and Perlmutter, 2008). For instance in writer's cramp, the act of handwriting induces an abnormal hand posture. This task specificity may be observed in other types of focal dystonia such as pianist's cramp, typist's cramp and other cramps, known as occupational dystonias. Conversely, generalized, primary dystonia is classified according to age at onset, and correlated with the body part affected. Recent advances in genetics revealed a strong inherited basis for a number of this heterogeneous group of disorders. Indeed, an increasing number of monogenic forms of primary dystonia have now been recognized (Ozelius and Bressman, this issue; see also Müller, 2009; Brüggemann and Klein, 2010). Studies in humans affected with dystonia have identified widespread dysfunction of neural systems, but have not substantially clarified the nature of the primary defect. Pathologically, there is no clear evidence for neurodegeneration in human postmortem samples examined (see Standaert, 2011), suggesting that dystonia can be considered as a motor circuit disorder, rather than an abnormality of a specific brain region.

More specifically, converging evidence from animal and human studies suggest that abnormal plasticity is a key factor in the pathophysiology of dystonia (Rothwell and Huang, 2003; Quartarone et al., 2003, 2006a; Weise et al, 2006; Martella et al., 2009; Peterson et al., 2010).

Long term potentation (LTP) and the converse process of long-term depression (LTD) are the most widely recognized physiological models of plasticity in the mammalian brain (Bliss and Gardner-Medwin, 1973). LTP has been originally studied in a variety of species, ranging from mice (Nosten-Bertrand et al., 1996) to monkeys (Urban et al., 1996); however in the last few years, LTP phenomena have been investigated also in humans using several translational model of plasticity at a system level (Ziemann et al., 2008; see also Hallett, 2011).

An interesting observation is that loss of synaptic plasticity has been described in hereditary dystonia, regardless of clinical penetrance (Edwards et al., 2006) and even in unaffected body parts of focal dystonia patients (Quartarone et al., 2008), suggesting that altered synaptic processes can represent a susceptibility factor, or an endophenotypic trait of dystonia.

In this article, we provide a survey of the evidence collected from studies performed from both mice and human subjects, which suggests that a key pathogenic element in dystonia is represented by the loss of synaptic homeostasis both at cellular, and system level, that lead to enhanced plasticity and motor dysfunction.

Bidirectional plasticity at striatal synapses: basic concepts

The basal ganglia include different interconnected subcortical nuclei that are involved in critical motivation, motor planning, and procedural learning function (Graybiel et al., 1994; Packard and Knowlton, 2002).

The striatum is the major input area of the basal ganglia, subserving a central role in planning and execution of motor programs (Graybiel et al., 1994; Kreitzer and Malenka, 2008; Jin and Costa, 2010). A complex interplay of the actions of distinct neurotransmitters is involved in the input, processing and output activity of this brain region (Lovinger, 2010).

Corticostriatal fibers utilize glutamate as a transmitter, representing the major excitatory input to the basal ganglia (Reubi and Cuenod, 1979). The striatum is also the recipient of the nigrostriatal dopaminergic projection, thus representing a site of input integration and selection of efferent information (Bolam et al., 2000).

Use-dependent long-lasting changes in synaptic efficacy at corticostriatal synapses have been proposed as a model for motor learning and memory. Pioneering work established that high-frequency stimulation (HFS) of corticostriatal glutamatergic afferents, using three trains of pulses at 100 Hz, 3 sec each, 20 sec apart, in association with postsynaptic neuronal firing, induces a long-lasting decrease in synaptic strength, referred to as LTD. This same induction protocol, but in the absence of external magnesium ions optimizes the induction of LTP, which, unlike LTD, is dependent on NMDA receptor activation (Fig. 1; Calabresi et al., 1992a,b). In whole-cell recordings, a similar phenomenon can be observed, as HFS (100 Hz, 1 sec, 4 trains) coupled to depolarization of the postsynaptic neuron reliably induces LTD at corticostriatal synapses (Lovinger et al., 1993; Walsh, 1993). Both corticostriatal LTD and LTP are recorded from the most common type of striatal cell, the medium-sized spiny neuron (MSN). This neuronal subtype represents more than 90% of the entire striatal cell population and is the only cell type projecting out of the striatum, thus playing a central role on the activity of the whole circuit (Bolam et al., 2000).

Once established, LTP can be reversed to control levels by a low-frequency stimulation protocol, a phenomenon termed “synaptic depotentiation” (Fig. 1; SD). SD is effectively induced by low-frequency afferent stimulation (2 Hz, 15 min). It has been hypothesized that if striatal LTP promotes the formation of motor memory while depotentiation represents a cellular mechanism aimed at erasing unnecessary synaptic information (Stäubli and Chun, 1996; Picconi et al., 2003; Martella et al., 2009).

In the recent past, there has been a progressive advance in our understanding of the properties and mechanisms underlying striatal LTD, LTP and SD. A complex cascade of biochemical processes follows the activation of glutamatergic and dopaminergic postsynaptic receptors and their interaction with presynaptic elements. The involvement of different neurotransmitter systems appears to be a peculiar feature of striatal plasticity, as compared to cerebellar or hippocampal plasticity (Lovinger, 2010). In addition, striatal interneurons have been shown to influence the polarity of long-term synaptic changes (Fino et al., 2008). In spite of the intrinsic nature of acetylcholine innervation, cholinergic interneurons profoundly affect synaptic activity and plasticity of MSNs (Pisani et al., 2007). There is indeed robust evidence to suggest that acetylcholine, through the activation of muscarinic receptors, is a major modulator of the induction process (Bonsi et al., 2008).

In slice preparations, LTD and LTP can be elicited by HFS, but also as a result of timed pairing between activation of pre- and post-synaptic neuronal elements (spike-timing-dependent-plasticity, STDP) (Fino et al., 2005; Shen et al., 2008). Indeed, the temporal relationship between presynaptic and postsynaptic activity has been shown to represent a key element that can govern the induction of activity-dependent long-term synaptic plasticity. By applying a suprathreshold depolarizing pulse either before or after the stimulation of cortical afferents, Fino and coworkers found that corticostriatal synapses express an “atypical” STDP, disrupting the “STDP rule” observed in other brain areas. Indeed, LTP could be elicited when the postsynaptic firing of the MSN neuron preceded cortical stimulation, whilst LTD was observed when a postsynaptic action potential was triggered in a MSN after cortical stimulation (Fino et al., 2005). A reversed STDP rule at corticostriatal synapses is likely to reflect the peculiar anatomical and functional characteristics of the striatum. In fact, MSNs are inhibitory GABAergic neurons, possessing a rich and tridimensional dendritic harborization and, in vivo, can oscillate between “up” and “down” states, resulting in large fluctuations of resting membrane potential (Stern et al., 1997).

Different microstimulation protocols have been developed more recently in order to obtain a more discrete activation of corticostriatal excitatory synapses. Some discrepancies emerged from these studies, as compared to the early work performed with traditional techniques, especially in respect to the role played by specific dopamine receptor subtypes in the induction and maintenance of LTD and LTP. A major issue is whether corticostriatal glutamatergic synaptic plasticity is expressed uniformly in both MSNs of the direct or indirect pathway,