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Invited review

Spinal inhibitory circuits and their role in motor neuron degeneration

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ABSTRACT

In the spinal cord neuronal activity is controlled by the balance between excitatory and inhibitory neurotransmission, mediated mainly by the neurotransmitters glutamate and GABA/glycine, respectively. Alterations of this equilibrium have been associated with spinal motor neuron hyperexcitability and degeneration, which can be induced by excitotoxicity or by decreasing inhibitory neurotransmission. Here we review the ventral horn neuronal network and the possible involvement of inhibitory circuits in the mechanisms of degeneration of motor neurons characteristic of amyotrophic lateral sclerosis (ALS). Whereas glutamate mediated excitotoxicity seems to be an important factor, recent experimental and histopathological evidence argue in favor of a decreased activity of the inhibitory circuits controlling motor neuron excitability, mainly the recurrent inhibition exerted by Renshaw cells. A decreased Renshaw cell activity may be caused by cell loss or by a reduction of its inhibitory action secondary to a decreased excitation from cholinergic interneurons. Ultimately, inhibitory failure by either mechanism might lead to motor neuron degeneration, and this suggests inhibitory circuits and Renshaw cells as pharmacologic targets for ALS treatment.

1. Introduction

Many neurological and psychiatric diseases have been associated with alterations of synaptic transmission, mainly dysregulation of the balance excitation/inhibition. When such alterations occur by a decrease of inhibitory neurotransmission or an increase of excitatory neurotransmission, the result is an overexcitation of the involved neuronal circuit, which can trigger a degenerative process by excitotoxicity, finally causing neuronal death and irreversible functional damage, giving rise to symptoms according to the neuronal area affected. In mammals, excitatory and inhibitory neurotransmission in the CNS are mediated mainly by glutamate and GABA, respectively, and because the main and common feature of this damage is the neuronal circuit overexcitation, most studies on excitotoxicity have focused on an excessive glutamatergic transmission, as may be the case in epilepsy. However, alterations of inhibitory mechanisms may lead also to functional deficits or neurodegeneration, as has been postulated for some kinds of epilepsy, absence seizures, drug-withdrawal syndromes, schizophrenia, autism and amyotrophic lateral sclerosis (ALS).

In the case of ALS, several genetic mutations have been described as the cause of the disease, but these represent only about 10% of ALS, the familial ALS (FALS). In the remaining 90% of cases the etiology is unknown (sporadic ALS, SALS), although some recent findings of alterations in genes and proteins in both FALS and SALS have challenged this vision, as will be pointed out below. The symptoms and progression of the disease are similar in FALS and SALS, suggesting a common pathway for motor neuron degeneration in both situations.

Among the mutations that have been linked to FALS the most prominent are in the superoxide dismutase 1 (SOD1) gene (about 20% of the cases), but there are more than one hundred related mutations described. These include genes involved in RNA processing, such as TDP43 (TAR DNA-binding protein 43), FUS (fused in sarcoma) and senataxin, and also repeat expansions, such as in C9ORF72 (chromosome 9 open reading frame 72), as well as mutations in genes involved in protein homeostasis, such as ubiquilin 2 and optineurin, or in cytoskeleton and cellular transport, mainly dynactin 1, profilin 1 and vesicle-associated membrane protein-associated protein B and C (for reviews see Chen et al., 2013; Pasinelli and Brown, 2006; Robberecht and Philips, 2013). Furthermore, some recent findings suggest that SALS could be a proteinopathy. For example, aggregates of misfolded SOD1, FUS, TDP43, optineurin, ubiquitin 2 and C9ORF72 have been found in

Abbreviations: ALS, amyotrophic lateral sclerosis; SOD1, superoxide dismutase type 1; FALS, familial amyotrophic lateral sclerosis; SALS, sporadic amyotrophic lateral sclerosis; CPG, central pattern generator; $GABA_AR$, GABA A receptor; $GABA_BR$, GABA B receptor; GlyR, glycinergic receptor; ChAT, choline acetyltransferase.

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motor neurons of some SALS patients (Bosco et al., 2010; Blokhuis et al., 2013).

The main pathological characteristic of both FALS and SALS is the degeneration of motor neurons in the cerebral cortex and in the spinal cord, and still there is an incomplete understanding of the mechanisms of this selective neuronal death. Glutamate-mediated excitotoxicity linked to several factors, such as inflammatory events, axonal transport deficits, oxidative stress and mitochondrial dysfunction, have also been proposed to play a role in the etiology of this disease (for reviews see Cleveland and Rothstein, 2001; Corona et al., 2007; Santa-Cruz et al., 2012). However, alterations of inhibitory circuits leading to hyperexcitability and excitotoxicity have been also proposed as a mechanism of motor neuron degeneration in ALS (Eisen and Weber, 2000; Petri et al., 2006, 2003; Vucic et al., 2009). The purpose of this paper is to review the state of the art on such possible mechanisms, including the neurochemistry and the cytoarchitecture of the inhibitory circuits in the mammalian spinal cord, and the experimental evidence of their role in motor neuron degeneration, focusing on the participation of Renshaw cells in motor neuron death in ALS.

2. Local neuronal circuits in the ventral spinal cord

Before describing the known inhibitory network alterations in ALS, we will briefly review the main components of neuronal networks in the spinal cord involved in the excitation, control, coordination and activity of muscles by motor neurons.

Spinal networks are circuits formed by several kinds of cells, such as neurons or non-neuronal cells. One of the most important components are the interneurons, mainly inhibitory, which are the most abundant neurons in the spinal cord and are closely involved in the generation and coordination of several locomotor patterns, such as left-right alternating activity. Based on the expression of transcription factors, these cells have been classified in eleven classes: dI1 to dI6, V0 to V3, VMV (Tanabe and Jessell, 1996). Most of these classes have an excitatory neurotransmitter phenotype, and only some classes (like V2b, $V0_{C/G}$, $V0_D$, and $V0_V$) have an inhibitory phenotype (Gosgnach, 2011), although they represent the majority of the spinal neuronal population. These interneurons participate in local intrasegmental circuits and also can project axons to other segments. The most studied interneuron is the Renshaw cell, because it is the only interneuron that receives afferents directly from motor neurons and mediate recurrent inhibition to them, through the production and co-release of GABA and glycine (Chang and Martin, 2009; McIntire et al., 1997; Sagne et al., 1997; Schneider and Fyffe, 1992; Todd and Sullivan, 1990). The role of Renshaw cells in excitation and motor neuron degeneration will be addressed later.

Spinal interneurons V0, V1, V2 and V3 are classified in subpopulations: V0 is subdivided in ventral $V0_V$, dorsal $V0_D$, cholinergic $V0_C$ and glutamatergic $V0_G$ interneurons. Localization of each kind of interneuron has been associated with its function. $V0_D$ are inhibitory commissural neurons that control left/right alternation (Lanuza et al., 2004), and V2 linage is divided in excitatory (V2a), inhibitory (V2b) (Karunaratne et al., 2002; Kimura et al., 2008; Lundfald et al., 2007; Peng et al., 2007) and V2c neurons (Panayi et al., 2010). V2a regulate burst robustness and left-right coordination during motor patterns, but the function for V2b and V2c remain to be identified. V3 are ventral (V3v) and dorsal ($V3_D$), commissural excitatory interneurons, each one with different electrophysiological properties, that distribute excitatory drive towards both halves of spinal cord, maintaining a regular and balanced motor rhythm during walking (Grossmann et al., 2010; Zhang et al., 2008).

2.1. Central pattern generators

Spinal neuronal networks have been organized in a model for its study and understanding, known as central pattern generators (CPG), which are delimited neuronal networks that generate the timing, phasing, and intensity cues to drive motor neuron output for simple rhythmic behaviors such as locomotion, mastication, and respiration (Harris-Warrick, 2011). In mammals each CPG performs two basic actions, 1) generate basic intrinsic discharge rhythms, and 2) shape and coordinate the pattern of activity of multiple motor neuron pools (Frigon, 2012). CPG patterns can be controlled voluntarily, such as scratching. However, it is known that scratching can be evoked by electrical stimulation in decerebrate animals (Deliagnina et al., 1975), showing that the spinal cord has intrinsic circuits needed for the motor behavior in the absence of cortical, subcortical or descending pathways, and that CPGs can produce rhythms autonomously without inputs from supraspinal or peripheral sources.

The spinal CPG circuitries are activated mainly by excitatory neurotransmission mediated by glutamate, and their excitation is controlled by inhibitory neurotransmission mediated by GABA and glycine, and also modulated by other neuromodulators, including serotonin, noradrenaline, dopamine, and peptides (mainly substance P) that act on metabotropic receptors; other neuromodulators, such as purines (ATP and adenosine), D-serine, endocannabinoids and nitric oxide, may be also involved in this regulation. This complex regulation endows the CPGs with an infinite range of output configurations, that confers the ability to generate a variety of rhythms used during various forms of locomotion, such as forward walking, backward walking, jogging, and running (Frigon, 2012; Grillner and Jessell, 2009; Harris-Warrick, 2011; Miles and Sillar, 2011).

2.2. Spinal cord neurotransmitters

Spinal cord circuits receive glutamatergic excitatory neurotransmission from two sources: first, inputs from descending tracts, such as the corticospinal tract whose fibers originate directly from pyramidal neurons of the motor cortex, basal ganglia circuits, and sensory fiber afferents. The second glutamatergic pathway is intraspinal, mainly from interneurons localized in the dorsal horn, commissural area, and nearby motor neurons (Brownstone and Bui, 2010). Axons of spinal origin or descending pathways project along the surrounding white matter and enter the cell body-rich gray matter area at subpopulation-specific sites. Descending and sensory pathways enter the spinal cord dorsally, while cholinergic afferents derive from intraspinal interneurons (interneurons V0c).

Spinal inhibition is mediated by GABA and glycine. These neurotransmitters are released inside the spinal cord from interneurons of class V1, V0 and V2b. V1 class include Ia inhibitory interneurons and Renshaw cells (Alvarez et al., 2005), whereas V0 and V2b interneurons are localized in the commissure (Brownstone and Bui, 2010; Lanuza et al., 2004). Some inhibitory interneurons, such as group II and commissural interneurons, receive inputs from reticulospinal pathways (Bannatyne et al., 2009; Jankowska et al., 2003).

Glutamatergic, GABAergic and glycinergic fast synapses are activated during locomotor network operation through their ionotropic postsynaptic receptors ($GABA_AR$ for GABA, NMDAR and AMPAR for glutamate and GlyR for glycine). However, these neurotransmitters also activate metabotropic receptors located both pre- and postsynaptically ($GABA_BR$ for GABA and group II and III mGluRs for glutamate). In isolated rodent spinal cord the initiation of motor neuronal pattern activity depends on the activation of ionotropic receptors, whereas its modulation involves mGluRs by