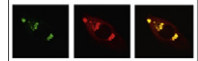


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Research Report

Cervical response among ascending ventrolateral funiculus pathways of the neonatal rat

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ABSTRACT

Propriospinal pathways, consisting of axons from interneurons that project to other spinal segments, have been implicated as likely candidates to mediate interlimb coordination in developing and adult mammals during quadrupedal locomotion. The superficial thoracic ventrolateral funiculus (VLF) contains both ascending and descending axons, and when stimulated can induce alternating rhythmic locomotor-like activity in the lumbar ventral roots of the isolated neonatal rat spinal cord. The goal of this work was to characterize the synaptic inputs onto cervical neurons from ascending axons in the VLF. Sprague-Dawley rats (P4–P7) were deeply anesthetized with halothane and their spinal cords were isolated, removed, and maintained *in vitro*. Intracellular recordings were made from 68 cervical (C5–C7) neurons having 71 latency classifications in response to thoracic VLF stimulation. Antidromic ($n=35$), monosynaptic ($n=2$), di- or tri-synaptic ($n=18$) and long-latency polysynaptic ($n=16$) responses were recorded. Recordings from reduced preparations (mid-sagittal section at C5–C7) suggest that much of the delay in the long-latency polysynaptic responses require a bilaterally intact cervical spinal cord. Fifty-three percent (17/32) of the VLF responsive cervical interneurons tested also exhibited long latency excitatory responses to lumbar dorsal root stimulation suggesting that many of the cervical VLF responsive interneurons receive indirect input from lumbar primary afferents. We hypothesize that the VLF contains a population of ascending axons originating from lumbar propriospinal interneurons that can influence cervical inter- and motoneurons. These ascending VLF axons may participate in interlimb coordination by providing moment-by-moment feedback to the cervical enlargement of lumbar central pattern generator and/or hindlimb proprioceptive activity.

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1. Introduction

Locomotion is a task requiring complex neural circuitry to effectively coordinate the activities of multiple limb and

trunk muscles acting across multiple joints simultaneously to accomplish smooth, uninterrupted over-ground propulsion. To accomplish this task, continuous tripartite interactions are required: (1) interneuronal spinal (central) pattern

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generators (CPGs); (2) descending command signals mediated largely by reticulospinal axons; and (3) sensory feedback from active body parts (Grillner 1985; Mori et al. (1977)).

Both Sherrington (1910) and Brown (1911) demonstrated the importance of intrinsic spinal cord circuitry in generating alternating hindlimb stepping movements in decerebrate and/or deafferented preparations. Distinct and independently controlled CPG networks for fore- and hindlimb movement are thought to exist in quadrupeds (Ballion et al. 2001; Juvin et al., 2005, 2007, 2012; Viala and Vidal, 1978). Coordination between regional CPG networks is thought to be mediated by long propriospinal axons and/or a series of local circuit interactions which couple cervical and lumbar activity during quadrupedal locomotion (Ballion et al. 2001; Cazalets and Bertrand 2000; English et al., 1985; Juvin et al., 2005, 2012; Miller et al. (1973, 1975); Zaporozhets et al., 2011). Cowley and Schmidt (1997) reported the development of rhythmic activity in the lumbar spinal cord in response to 5-HT/NMA applied to the cervical or cervicothoracic segments and this group recently demonstrated that the propriospinal system, in isolation, is sufficient to activate the locomotor network (Cowley et al., 2010, 2009, 2008). In the isolated *in vitro* neonatal rat spinal cord preparation, Ballion et al. (2001) demonstrated that when disconnected, separate spinal enlargement rhythms persist and either the cervical or lumbar neural networks are capable of driving the thoracic (T3–T10) circuitry at their inherent frequencies. They concluded that functional interactions between the regional CPGs produce a coordinated pattern of bursting with an intermediate cycle period. Juvin et al., 2005 confirmed the functional independence of fore- and hindlimb CPG networks, but found that while the lumbar generators could drive their cervical counterparts via intact propriospinal circuitry, the reverse was not possible. Contrary to Ballion et al. (2001), Juvin et al. (2005) concluded that a caudorostral propriospinal excitability gradient exists, and that it is this asymmetrical connectivity, and not differences in the inherent rhythmogenic capacities of the two spinal enlargements, which mediate interlimb coordination. More recently, Juvin et al. (2012) provided further evidence that both long-projecting propriospinal as well as interposed midthoracic segments make contributions to inter-CPG coupling. Despite differences between their functional interpretations of CPG-mediated coordination, neither Ballion et al. (2001) or Juvin et al. (2005, 2012) attempted to identify the anatomical location(s) of the inter-enlargement pathways responsible for their divergent conclusions. Cowley et al. (2009) suggested that locomotor-related commissural projections are redundantly distributed along a bi-directional gradient with the thoracolumbar junction (T13–L1) being of particular importance; while Dutton et al. (2006) identified bilateral long ascending propriospinal projections from lumbosacral neurons to the upper cervical spinal cord with a contralateral predominance in the adult rat. Again, identification of the anatomical location(s) of pathways responsible for these conclusions was not established.

In mammals, it is known that descending ventrolateral funiculus (VLF) fibers play important roles in the initiation of locomotion (Jordan, 1986; Noga et al., 1991; Steeves and Jordan, 1980). VLF axons in 1–6 day old neonatal rats have been shown to project both ipsilaterally and contralaterally to

lumbar interneurons and motoneurons via reticulospinal and propriospinal pathways (Pinco and Lev-Tov, 1994). However, more recent studies question whether discrete white matter tracts within the VLF carry the sole responsibility for the initiation of spontaneous locomotion as had been previously suggested (Brustein and Rossignol, 1998; Cowley et al., 2010; Loy et al., 2002a,b; Sholomenko and Steeves, 1987; Vilensky et al., 1992). In adult cats, it is known that long term deficits in homolateral fore- and hindlimb coupling persist even following the recovery of the locomotor and postural deficits resulting from mid-thoracic VLF and ventral lesions (Bem et al., 1995; Brustein and Rossignol, 1998). Both thoracic spinal VLF-ventral column and VLF-dorsolateral funiculus demyelination lesions induced notable deficits in adult rat hindlimb/forelimb coordination without abolishing over-ground locomotor capabilities (Loy et al., 2002a,b). These interlimb deficits became more pronounced during attempts to increase the rate of locomotion (Loy et al., 2002a,b).

Miller et al. (1973) concluded that long ascending propriospinal pathways can be influenced by hindlimb nerve stimulation, bilaterally, and that monosynaptic, ipsilateral ascending VLF projections dominate the contralateral disynaptic projections. Axon collaterals to various rostral spinal cord segments have also been reported from the lumbosacral enlargement (Riddell et al., 1994). Grottel et al. (1998) reported that some sacral (S1 and S2) neurons have single, double, and triple projections to the cervical enlargement, cerebellum, and the reticular formation. Such divergence of any ascending tract neurons had not been previously reported, and it is significant to note that nearly half of the neurons within their study had both propriospinal and supraspinal projections. Similar studies (Grottel et al., 1999; Krutki et al., 1998, 1997; Mrowczynski et al., 2001) in the cat have revealed larger than anticipated numbers of bi-directional lamina VII and VIII C6/C7 neurons sending ascending projections to the cerebellum and/or lateral reticular nucleus and descending projections to thoracic, lumbar, and/or sacral levels. Among C6/C7 cells classified as purely propriospinal, various branching patterns (ipsi-, contra-, or bilateral) at multiple caudal spinal levels were reported. It was concluded that as a result of such diversified branching patterns, the same information regarding limb activity could be relayed to many different spinal and/or supraspinal centers. Evidence for propriospinal pathways capable of propagating the locomotor command signal has recently been demonstrated (Courtine et al., 2008; Cowley et al., 2010, 2009; Juvin et al. (2012) and our laboratory has identified the VLF as containing many of these inter-enlargement pathways in the adult rat (Reed et al., 2006).

Afferent input from hip position and the unloading of the limb play crucial roles in determining the transition from stance to swing phase in the step cycle (Kriellaars et al., 1994). In real stepping, proprioceptive signals regarding limb movement and pertinent spinal reflexes must be processed by spinal and supraspinal networks in order for appropriate regional CPG-coupling to occur (Andersson and Grillner, 1981, 1983; Conway et al., 1987; Edgerton et al., 2008). Stimulation of lumbar afferents have recently been shown to have the capability to bypass lumbar locomotor generators and directly access cervical CPG circuitry; unlike cervical afferent stimulation which requires active intervention of

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