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Review

Insulin-like growth factor 1 in diabetic neuropathy and amyotrophic lateral sclerosis

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ABSTRACT

Insulin-like growth factor 1 (IGF-1) is a pluripotent growth factor with multiple functions in the peripheral and central nervous system. It supports neuronal survival and axon growth, and also acts on myelinating Schwann cells and oligodendroglia. The biological functions of IGF-1 are modulated by IGF-binding proteins (IGFBPs). Expression of IGF-1 and its corresponding IGF-1 receptor (IGF-1R) are dysregulated in patients with diabetes and neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). IGFBP5, an inhibitory binding protein for IGF-1, is also substantially increased in nerve biopsies of patients with sensorimotor diabetic neuropathy (DNP). We investigated the pathogenic relevance of this finding in transgenic mice overexpressing IGFBP5 in motor axons and sensory nerve fibers. These mice develop motor axonopathy and sensory deficits similar to those seen in DNP. Motor axon degeneration was also observed in mice in which IGF-1R was conditionally depleted in motoneurons, indicating that reduced activity of IGF-1 on IGF-1R in motoneurons is responsible for the observed effect. The upregulation of IGFBP5 has possibly contributed to the lack of efficacy found in previous clinical trials with systemically administered IGF-1 in patients with other forms of motoneuron disease such as ALS. Thus, strategies aiming at circumventing these inhibitory effects could be of benefit for development of new therapies for ALS and DNP. However, these strategies have to be built on a better understanding of the metabolic processes that contribute to neurodegeneration, and on the role of IGF-1 in these metabolic processes that go beyond protection from axonal degeneration and cell death.

Contents

1. Physiologcal functions of IGF-1 in the motor system

The insulin-like growth factors IGF-1 and IGF-2 are trophic factors for many types of neurons whose growth-promoting actions are mediated *via* the insulin/insulin-like growth factor receptor family. Their biological functions are modulated by six insulin-like growth factor binding proteins (IGFBPs) (Bach et al., 2005; De Meyts and Whittaker, 2002; Duan, 2002; Fernandez and Torres-Aleman, 2012; Firth and Baxter, 2002; Hwa et al., 1999). IGF-1 mediates its neurotrophic effect *via* the IGF-1 receptor (IGF-1R) (Bonni et al., 1999; Brunet et al., 1999; Cui et al., 2005; Feldman et al., 1997; Kim and Feldman, 1998; LeRoith et al., 1995), and promotes neuronal survival, neurite formation and outgrowth in sensory, sympathetic and motoneurons (Arakawa et al., 1990; Hughes et al., 1993; Ishii et al., 1994; Pu et al., 1999; Recio-Pinto and Ishii, 1988; Russell and Feldman, 1999; Thoenen et al.,

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1993; Vergani et al., 1998; Zackenfels et al., 1995). IGF-1 was found to reduce programmed cell death of motoneurons *in vivo* during development, following axotomy or spinal cord transection (Contreras et al., 1995; Houenou et al., 1994; Hughes et al., 1993; Neff et al., 1993; Rabinovsky et al., 2003). In addition to its survival effect on axotomized motoneurons, IGF-1 increases terminal sprouting in axons, accelerates functional recovery of injured nerves, overcomes cycloheximide-mediated inhibition of sciatic nerve regeneration after crush lesion, and attenuates peripheral motoneuropathies induced by chemotherapeutic agents such as vincristine (Caroni and Grandes, 1990; Cheng et al., 1996; Lewis et al., 1993; Pu et al., 1995).

However, the effects of IGF-1 are not confined to neurons. In peripheral nerves IGF-1 is mainly expressed in Schwann cells of postnatal rodents, and promotes Schwann cell survival, proliferation, differentiation and neuronal fiber myelination (Cheng et al., 1999; Syroid et al., 1999; Ye et al., 2002). These Schwann cell-mediated effects are critical for appropriate neuronal signaling and peripheral nervous system function. The importance of IGF-1 in promoting the health and connectivity of the peripheral nervous system is underlined by findings in *Igf-1* deficient mice showing profound alterations in motor- and sensory nerve conduction velocities and impaired A-fiber responses in sciatic nerves (Gao et al., 1999). Furthermore, a shift towards smaller axonal diameters but unchanged number of myelinated fibers and g-ratio were found in *Igf-1* deficient sciatic nerves (Gao et al., 1999). Replacement therapy with exogenous recombinant IGF-1 restored both motor- and sensory nerve conduction velocities (Gao et al., 1999).

Igf-1 deficient mice also exhibit a marked loss of axon density in the corticospinal tract. Especially, the dorsal funiculus is reduced in size, suggesting that IGF-1 is involved in regulating the outgrowth of axons and/or survival of corticospinal motoneurons (Liu et al., 1993; Ozdinler and Macklis, 2006). Corticospinal neurons also react to IGF-1 with enhanced axon growth (Ozdinler and Macklis, 2006). IGF-1 is present in the neonatal gray matter and together with a decreasing gradient of Wnt1 and Wnt5a (Liu et al., 2005) it guides axon elongation of corticospinal neurons towards the spinal cord. On the other hand it is not fully resolved, whether IGF-1 plays a physiological role for survival of developing cortical neurons. During embryogenesis and early postnatal periods, neuronal cell death is observed in the developing cortex (Nikolic et al., 2013). Apoptosis is mostly found in the ventricular zone where neuronal and glial precursor cells are mitotically active (Malatesta et al., 2003). When major regulators of apoptosis such as Caspase-3 (Kuida et al., 1996) or Apaf 1 (Cecconi et al., 1998) are depleted, massive overgrowth of the brain is observed, so that it even outgrows the skull. Cell death is also observed at early postnatal stages (Naruse and Keino, 1995). About 30% of neuronal cells seem to be eliminated during this period, in particular in layer II, III and IV of the early postnatal cortex. In a transgenic mouse model in which IGF-1 is overexpressed under the Nestin promoter in developing and postnatal neurons, a more than 40% reduction of neuronal cell death was observed in the population of cerebellar granule cells, and also the total volume of the cortex was increased by about 30% (Hodge et al., 2007). This apparently reflected reduced cell death of cortical neurons (Hodge et al., 2007), but also enhanced neurogenesis (Hodge et al., 2004; Popken et al., 2004). However, it is still not fully resolved, whether these findings with transgenic overexpression of IGF-1 in the nervous system represent a physiological function of IGF-1 in the developing and early postnatal brain. The number of spinal cord motoneurons seems to be unaffected in 2 months old *Igf-1* deficient mice (Beck et al., 1995). Knockout of the IGF-1 receptor is embryonic lethal, demonstrating how vital the IGF-1 signaling system is for development (Bondy and Lee, 1993; Bondy et al., 1992; Bondy, 1991; Liu et al., 1993).

2. IGF-1 and diabetic neuropathy

Diabetic neuropathy is one of four major complications in about 50% of *diabetes mellitus* patients and appears earlier and more frequently than the other three — retinopathy, nephropathy and cardiomyopathy (Alberti and Zimmet, 1998; Boulton, 1998). Diabetic neuropathy develops in peripheral sensory, motor and autonomic nerves and becomes in most cases apparent as a polyneuropathy, which causes sensory and motor disturbances, dysautonomia, and bathyanesthesia (Polydefkis et al., 2003; Said, 2007; Strotmeyer, 2008; Vinik et al., 1992). Life quality is further reduced by chronic pain sensations, which occur in about one quarter of patients with diabetic neuropathy (Quattrini and Tesfaye, 2003). Painful diabetic neuropathy is characterized by spontaneous pain, mechanical hyperalgesia, and tactile allodynia (Tesfaye, 2009). It is accompanied by functional and neurochemical changes at peripheral nerves, spinal cord, and supraspinal pain control areas (Morgado and Tavares, 2007; Morgado et al., 2010; Selvarajah et al., 2006; Selvarajah et al., 2008; Sima, 2003). Several factors have been proposed to contribute to the development of diabetic polyneuropathy, including perturbed blood flow, oxidative stress, accumulation of advanced glycation end products and altered expression of growth factors. Thus, treatment strategies appear complex (Clements, 1979) and understanding the pathophysiology of neuropathy in *diabetes mellitus* patients appears as a prerequisite to devise effective treatments. Previous studies have reported that reduced levels of circulating IGF-1 are a common feature in patients with diabetes, with the highest reductions observed at older age and with longer duration of disease (Migdalis et al., 1995; Tan and Baxter, 1986). Similarly, in streptozotocin-treated rodents, a common animal model of diabetes, reduced IGF-1 expression levels were observed in peripheral nerves at early stages of disease, and progressive loss of motor fibers becomes apparent with age, with loss of distal axons occurring prior to proximal axons and motoneuron cell bodies (Ramji et al., 2007; Wuarin et al., 1994). In the same model, elevated renal insulin-like growth factor binding protein 5 (Igfbp5) levels were found, but the relevance of these findings for diabetic polyneuropathy remained unclear (Park et al., 1998). Recently, we investigated alterations of expression of IGFs and IGFBPs in peripheral nerves of patients with diabetic neuropathy and compared them with other neuropathies and healthy controls (Simon et al., 2015). IGFBP5 was highly upregulated in sural nerve biopsies of patients with sensorimotor diabetic neuropathy and was mainly localized in axons and the extracellular matrix surrounding the axons, indicating that it is produced in motoneurons, anterogradely transported and released into the extracellular space (Fig. 1). Thus, IGFBP5 could interfere with IGF-1 signaling derived both from the circulation and from contacting Schwann cells. Transgenic mice overexpressing *Igfbp5* (Bp5 tg+) in motor axons and sensory nerve fibers and conditional *Igf1r* knock-out (*cIgf1r ko*) mice lacking the receptor in the same populations of nerve fibers were generated to investigate the pathogenic relevance of this finding. Mice overexpressing Igfbp5 appear normal at birth and at younger ages. However, by 6 months of age, dysmyelination occurs. Similarly, the loss of motor fibers and motoneuron cell bodies was not detectable until 6 months of age (Fig. 2). Interestingly, dysmyelination was not observed in *cIgf1r ko* mice lacking the IGF-1R only in motoneurons, indicating that the observed defects in peripheral nerve myelination in Igfbp5-overexpressing mice are likely to be due to reduced IGF-1 function in Schwann cells. These motoneuron specific conditional *Igf1r* deletion mutants further revealed that axon maintenance is directly dependent on IGF-1R activation, since loss of large motor fibers in the phrenic, facial, and the mixed sciatic nerve was observed in the *cIgf1r ko* mice (Fig. 2) (Simon et al., 2015). Sensory axons appeared affected too, reflected by altered responses to heat, pain and mechanical stimulation in *Igfbp5* transgenic animals (Simon et al., 2015) and by enhanced dystrophy and degeneration of sensory nerve fibers (Fig. 3). Furthermore, *Igfbp5* transgenic mice showed reduced latency to fall from an accelerating rotarod, pointing to the involvement of proprioceptive neurons. Together with the altered thresholds for heat-sensing thermoreceptors, reduced substance P levels and reduced density of small fibers in the skin, classical signs of diabetic neuropathy