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Research Report

Differential Islet-1 expression among lumbosacral spinal motor neurons in prenatal mouse

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ABSTRACT

Onuf's nucleus in the lumbosacral spinal cord, comprising somatic motoneurons that innervate the pelvic floor muscles via the pudendal nerve, shares some characteristics with the autonomic preganglionic neurons and functions in coordination with the autonomic nervous system. In mouse, neurons projecting to the urethral sphincter and ischiocavernosus muscles form the dorsolateral (DL) nucleus at the caudal lumbar levels, whereas neurons projecting to the limb and hip joint muscles comprise the retrodorsolateral and ventral nucleus, as well as the DL nucleus at the rostral lumbar levels. The results of the present study in mouse revealed that the expression pattern of a LIM homeodomein protein Islet-1, an embryonic marker for motoneurons in the spinal cord, was different among motoneuronal groups at the prenatal stage (embryonic days 13.5–15.5); the highest expression was observed in the DL at the caudal lumbar cord, whereas there was little expression in the lateral part of the rostral DL. Islet-1 expression was also observed in the parasympathetic preganglionic neurons at the sacral spinal cord. These findings provide evidence that the DL neurons at the caudal lumbar cord, corresponding to Onuf's nucleus, are chemically distinct among the motoneuronal groups at the prenatal stages. This differential Islet-1 expression among the motoneuronal groups suggests that Islet-1 not only leads to a motoneuronal lineage, but also to the differentiation of motoneuronal subsets in the lumbosacral spinal cord.

1. Introduction

The lumbosacral spinal cord contains motoneurons associated with the autonomic functions of the pelvic organs, such as the micturition, defecation, and sexual behavior. The parasympathetic preganglionic neurons (PPNs) in the sacral intermediolateral (IML) column, which project to the pelvic ganglia that innervate the peripheral effectors, have a significant role in pelvic organ activity. The spinal PPNs send excitatory signals to contract the detrusor muscles in the bladder wall to void urine, to contract the large intestine, and to dilate the cavernous sinus of the penis, thereby inducing erection. These visceromotor functions are not conducted only by the autonomic nervous system, but are executed in coordination with the somatic motoneurons that innervate the pelvic floor muscles via the pudendal nerve. The motoneurons projecting to the pelvic floor muscles are located in the nucleus of Onuf (ON), mainly in the upper sacral spinal cord in mammals, including humans (Sato et al., 1978; Kuzuhara et al., 1980; Schrøder 1980; Ueyama et al., 1984, 1985, 1987; Roppolo et al.,

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1985; McKenna and Nadelhaft, 1986; Thor et al., 1989). In the rat, the ON homologue is located in two separated columns, i.e., the dorsolateral (DL) and dorsomedial (DM) groups (McKenna and Nadelhaft, 1986). ON neurons located in the DL division innervate the external urethral sphincter muscles, which relax in coordination with the contraction of the detrusor muscles. On the other hand, the ON neurons innervating the sphincter ani externus, are located in the DM division. The ischiocavernosus and bulbospongiosus muscles, which are involved in facilitating penile erection and ejaculation, are innervated by the DL and DM, respectively (McKenna and Nadelhaft, 1986; Ueyama et al., 1987). The DL and DM nuclei are sexually dimorphic in the rat, and the majority of their motoneurons are influenced by circulating steroid hormones, including testosterone (Breedlove and Arnold, 1981; Jordan et al., 1982; Kurz et al., 1991; Matsumoto 1997, 2001). In most other mammals; such as cat, dog, guinea pig, golden hamster, and monkey; the ON is located exclusively in the nucleus homologous to the DL in the rat (Sato et al., 1978; Kuzuhara et al., 1980; Ueyama et al., 1984, 1985; Roppolo et al., 1985; Thor et al., 1989; Gerrits et al., 1997a; Kuipers et al., 2004), whereas in the pig (Blok et al., 1996) and Mongolian gerbil (Ulibarri et al., 1995), the motoneurons projecting to the external anal sphincter muscle are located in a completely different position.

ON neurons have some peculiar characteristics. Their cell bodies are smaller than most other somatic motoneurons and they do not degenerate in patients suffering from amyotrophic lateral sclerosis, which destroys almost all somatic motoneurons (Mannen et al., 1977). On the other hand, ON neurons do degenerate in patients suffering from Shy-Dräger disease, which affects autonomic preganglionic neurons (Mannen et al., 1982; Chalmers and Swash, 1987). Furthermore, ON neurons are innervated by the paraventricular hypothalamic nucleus, which also projects to autonomic preganglionic neurons (Holstege, 1987). The descending serotonin projections, projecting preferentially to the autonomic preganglionic neurons in the intermediate zone, also have remarkably dense terminals in the ON (Micevych et al., 1986; Newton and Hamill, 1989). Therefore, the characteristics of ON neurons are between those of somatic and autonomic motoneurons.

The ontogeny of the ON neurons was examined particularly in the sexually dimorphic DM group of the rat. High testosterone levels in the postnatal period might reduce cell death of DM neuron in the male (Breedlove and Arnold, 1983; Segenlaub et al., 1989). On the other hand, the differentiation of the ON neurons and their migration into distinct subclasses in the earlier prenatal period is unclear, although the DM neurons are generated by E14 in the rat (Breedlove and Arnold, 1983). Autonomic preganglionic neurons and somatic motoneurons arise from a common progenitor population in the spinal cord. Soon after their generation, however, postmitotic motoneurons differentiate into distinct subclasses, and the preganglionic neurons migrate dorsally to settle in the IML. Molecular distinctions can be used to identify motoneurons prior to the migration period. Islets 1 and 2 (Isl-1, Isl-2), LIM homeodomein proteins, distinguish somatic motoneurons from preganglionic neurons at the thoracic level. Most somatic motoneurons express both Isl-1 and Isl-2, whereas the preganglionic neurons express Isl-1, but not Isl-2, by the time individual motoneurons have settled in their location in the chicken and mouse (Tsuchida et al., 1994; Thaler et al., 2004). Furthermore, motoneurons in the medial division of the lateral motor column (LMC) projecting to limb muscles derived from the ventral muscle mass express both Isl-1 and Isl-2, whereas those in the lateral division of the LMC projecting to limb muscles derived from the dorsal muscle mass express only Isl-2 at late embryonic stages in the chick (Tsuchida et al., 1994). Therefore, the expression pattern of Isl-1 and Isl-2 might define motoneuronal subclasses during the prenatal period. To examine whether the ON possesses any characteristics distinct from those of other motoneuronal groups during ontogeny, we primarily examined the prenatal expression of Islets in the lumbosacral spinal cord. To examine expression of Islets, we use antibody against Isl-1 and Isl-1/2. Therefore, the neurons immunoreactive for Isl-1/2, but negative for Isl-1 were considered to be those expressing only Isl-2. Further, the neurons negative for Isl-1 and Isl-1/2 were considered to be those devoid of Isl-1 and Isl-2. On the other hand, we could not distinguish the neurons expressing only Isl-1 from those expressing both Isl-1 and Isl-2 in the present study.

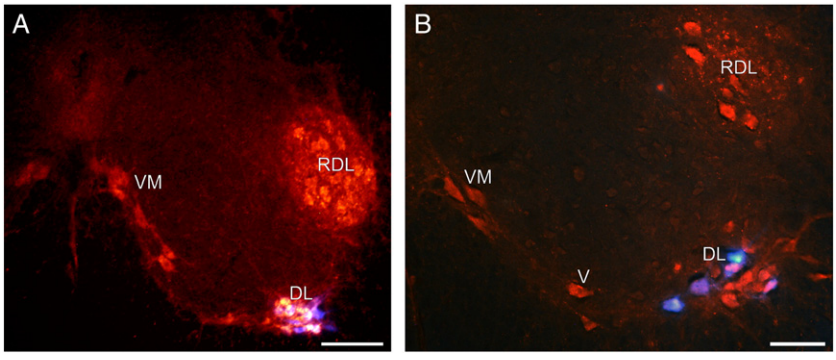

Fig. 1 – (A) In the ventral horn of the lumbosacral spinal cord of the adult, motoneurons of the RDL, the DL, and the VM were ChAT-immunoreactive (shown in red). The motoneurons in the DL were labeled after FB injection to the external urethral sphincter muscle (shown in blue). (B) The motoneurons of the RDL, the DL, the V and the VM were ChAT-immunoreactive (shown in red). The motoneurons in the DL were labeled after FB injection to the ischiocavernosus muscle (shown in blue). Doubly labeled neurons are shown in purple. Scale bars, 100 μm.