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Review

Whither motoneurons?

Robert M. Brownstone[a,*], *Douglas G. Stuart*[b]

[a]*Departments of Surgery (Neurosurgery) and Anatomy & Neurobiology, Dalhousie University, Halifax, NS, Canada B3H 1X5*
[b]*Department of Physiology, University of Arizona, Tucson, AZ 85721–0093, USA*

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ABSTRACT

In the preceding series of articles, the history of vertebrate motoneuron and motor unit neurobiological studies has been discussed. In this article, we select a few examples of recent advances in neuroscience and discuss their application or potential application to the study of motoneurons and the control of movement. We conclude, like Sherrington, that in order to understand normal, traumatized, and diseased human behavior, it is critical to continue to study motoneuron biology using all available and emerging tools.

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Contents

* *Corresponding author at:* Departments of Surgery (Neurosurgery) and Anatomy & Neurobiology, Dalhousie University, 14A Tupper Building, 5850 College Street, Halifax, NS, Canada B3H 1X5. Fax: +1 902 473 6852.
E-mail address: rob.brownstone@dal.ca (R.M. Brownstone).

Abbreviations: AHP, afterhyperpolarization; ALS, amyotrophic lateral sclerosis; CNS, central nervous system; SMA, spinal muscular atrophy; Chx10, visual system homeobox 2; En1, engrailed homeobox 1; Err3, estrogen receptor-related protein 3; GDNF, glial cell-derived neurotrophic factor; Gfrα1, GDNF family co-receptor α1; iPS, induced pluripotent stem (cells); NeuN, neuron-specific nuclear protein; Pitx2, paired-like homeodomain 2; SOD1, superoxide dismutase 1

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1. Introduction

When considering the historic content presented in the previous four articles of our sequence on the history of motoneuron neurobiology, it is interesting to consider two points of view. The first was illustrated in the classic 1976 Hollywood movie, "Gumball Rally".[1] At the outset of the trans-American car race, one of the characters removed his rearview mirror and said to his partner: "And now my friend, the first rule of Italian driving: what's behind me is not important." This contrasts with the philosophy of Sir Isaac Newton [1642–1727], perhaps first expounded upon by John of Salisbury [1115–1176] in 1159 (Turgeon, 1999), that we can see farther because we stand on the shoulders of giants. In science, it is likely that few investigators would side with the Gumball Rally philosophy! Furthermore, Bornmann et al. (2010) have recently presented evidence that the most highly cited papers are indeed built on the scientific knowledge of other highly cited papers (i.e., the works of "giants") (Bornmann et al., 2010). With this in mind, it behooves us to respect and profit from the whence of our preceding preface (Stuart et al., 2011) and four articles (Barbara and Clarac, 2011; Clarac and Barbara, 2011; Duchateau and Enoka, 2011; Stuart and Brownstone, 2011) and now discuss and provide examples of the whither of motoneuron neurobiology. Although applicable to many animal models (e.g. invertebrate, non-mammalian vertebrate, brainstem motoneurons), we focus here on the study of mammalian motoneurons and motor units.

2. Molecular biology tools

Over the past decade, the advent of molecular biological tools has led to an increase in our understanding of spinal motor systems. For the most part, these methodologies have been used to study spinal networks responsible for locomotor behavior (Brownstone and Bui, 2010; Fetcho et al., 2008; Kiehn, 2006). In large measure, these tools were developed directly as a result of our understanding of the molecular basis of normal mammalian spinal cord development. During development, specific transcription factors are expressed in sub-populations of spinal neurons. Through their understanding of these transcription factors, investigators have been able to (1) identify particular populations of interneurons to study using anatomical and physiological techniques (Wilson et al., 2005; Zagoraiou et al., 2009), and (2) modify the activity of these particular populations to study their roles in motor behavior (Crone et al., 2009; Gosgnach et al., 2006). These approaches have led to significant advances in the study of spinal cord networks.

Some interneurons identified in the above manner have been shown to project to and form synapses with motoneurons. For example, some V2a interneurons (identified by expression of Chx10) form excitatory synapses on motoneurons (Al-Mosawie et al., 2007; Lundfald et al., 2007), and some V1 interneurons (identified by expression of En1 and include Ia inhibitory interneurons and Renshaw cells) form inhibitory synapses on motoneurons (Alvarez et al., 2005; Sapir et al., 2004). In addition, a small population of cholinergic interneurons (identified by expression of the transcription factor Pitx2) near the central canal has been shown to modulate motoneuron activity by reducing their action potentials' post-spike afterhyperpolarization (AHP) via activation of post-synaptic muscarinic receptors (Miles et al., 2007; Zagoraiou et al., 2009). The addition of new trans-synaptic labeling techniques involving genetically modified rabies viruses promises to play a key role in the identification of last-order interneurons (Stepien et al., 2010). Thus, molecular biological techniques have clearly been important in the identification of excitatory, inhibitory, and modulatory inputs to motoneurons, and will thus promote increased understanding of the control of motoneuron activity during motor behaviors.

More recently, our understanding of motoneuron development has led to the possibility of identifying and manipulating particular classes of motoneurons. For example, gamma motoneurons down-regulate NeuN and express the transcription factor Err3 and the GDNF receptor, Gfrα1 (Friese et al., 2009; Shneider et al., 2009). The identification of this molecular specificity will allow the development of techniques to specifically identify and manipulate gamma motoneurons in order to better understand their function. Similar approaches will be important for future studies of, for example, the physiology of different subtypes of motoneurons, such as those innervating fast-twitch vs. slow-twitch muscle fibers, and the differential regulation of motoneurons innervating flexor vs. extensor muscles. Evidence that the latter are genetically distinct arises from the concepts that the electrophysiological properties of flexor-innervating motoneurons mature earlier than those of extensor-innervating motoneurons (Vinay et al., 2000) and that there are distinct regulatory genes involved in motor pool specification (Dasen et al., 2005). While the genetic tools for such sub-class specific manipulation have not yet been developed, as our understanding of motoneuron development increases, these new tools will surely become available.

3. In vivo imaging of activity and optogenetics

In addition to the ability to genetically identify and manipulate populations of neurons, we now have the capacity to use optical approaches to record activity, and activate or silence specific genetically-identified neurons. This topic has recently been reviewed in depth (Deisseroth, 2011; Knopfel et al., 2010). For the study of motoneurons, it will be important to translate these efforts so that specific light-sensitive molecules are expressed in particular sub-populations of motoneurons. Furthermore, to understand how these populations contribute to motor behavior, it will be important to develop in vivo preparations that can be used for the optogenetic study of motoneurons. There are several hurdles to be surmounted for this to occur. The first problem, which has recently been overcome for use with electrode-based recordings, is the development of a stable anesthetized preparation for spinal recording in mice (Manuel et al., 2009; Meehan et al., 2010).

[1] Written by Chuck Bail and Leon Capetanos, Warner Brothers Pictures.