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Review

From action potential to contraction: Neural control and excitation–contraction coupling in larval muscles of *Drosophila*

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ABSTRACT

The neuromuscular system of *Drosophila melanogaster* has been studied for many years for its relative simplicity and because of the genetic and molecular versatilities. Three main types of striated muscles are present in this dipteran: fibrillar muscles, tubular muscles and supercontractile muscles. The visceral muscles in adult flies and the body wall segmental muscles in embryos and larvae belong to the group of supercontractile muscles. Larval body wall muscles have been the object of detailed studies as a model for neuromuscular junction function but have received much less attention with respect to their mechanical properties and to the control of contraction. In this review we wish to assess available information on the physiology of the *Drosophila* larval muscular system. Our aim is to establish whether this system has the requisites to be considered a good model in which to perform a functional characterization of *Drosophila* genes, with a known muscular expression, as well as *Drosophila* homologs of human genes, the dysfunction of which, is known to be associated with human hereditary muscle pathologies.

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1. Introduction

The neuromuscular system is based on a complex interaction of many different components that cooperate to produce movement, i.e. force or displacement, in response to a stimulus generated in the central nervous system. The integrated function of the neuromuscular system can reach a high level of complexity, thus making the dissection of single operational components very difficult. In this respect, model organisms have historically contributed by offering less complicated systems in which it may be possible to identify the essential evolutionarily conserved components. In this respect, the neuromuscular system of *Drosophila melanogaster* has been studied for many years by virtue of its simplicity, and because it is accessible, with relative ease, to genetic manipulations.

In fact, in *Drosophila* it is possible to combine sophisticated genetic and molecular approaches with equally advanced behavioural, physiological and morphological investigational techniques. Since the completion of

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whole genome sequencing in a number of species, it has become increasingly apparent that there is a very high level of similarity of encoded sequences conserved throughout evolution. This is of particular interest when one considers genes that have been implicated in human genetic diseases. Approximately 75% of all human disease genes have been found to have highly conserved counterparts in *Drosophila* (Rubin et al., 2000). This finding has encouraged the use of *Drosophila* as a powerful model organism to be used in the characterization of evolutionarily conserved genes, many of which are thought to be involved in the pathogenesis of human hereditary diseases (Fortini et al., 2000; Chien et al., 2002). In this view it is important to underline the advantages provided, by the use of novel approaches such as those involving dsRNAi in order to produce the targeted silencing of the gene of interest in a tissue-specific or temporally-controlled manner using specific GAL4 drivers, thus allowing the functional characterization also of those genes which show embryonic lethality (Fortini et al., 2000; Link, 2001; Chien et al., 2002; Muqit and Feany, 2002; Driscoll and Gerstbrein, 2003; Pesah et al., 2004; Bilen and Bonini, 2005; Sang and Jackson, 2005; Chartier et al., 2006; Rockenstein et al., 2007; Benna et al., in press). Using this approach, important insights have been attained into the biological mechanisms leading to the appearance of neurodegeneration in Alzheimer's or Parkinson's disease, just to give two examples. In particular the application of this methodology was recently demonstrated to be useful in understanding the mechanisms of a human hereditary mitochondrial disease affecting the neuromuscular system (Zordan et al., 2006).

The simplicity of *Drosophila* as a model organism is, however, only apparent. The *Drosophila* neuromuscular system is indeed much simpler than the homologous mammalian system, but exhibits a high level of organization characterized by the presence of different types of muscles, each specialized to perform well defined functions (locomotion, jump, digestion, circulation etc). Moreover, the *Drosophila* life cycle is characterized by different stages (embryo, larva, adult) and transitional phases which, in the case of the larval-to-adult metamorphosis leads to dramatic changes in the organism as a whole, giving rise to an almost totally new body structure. The majority of the studies on *Drosophila* muscles have been done in adult flies, and few in larvae. This review aims to re-examine the available knowledge concerning the larval neuromuscular system, and to validate its use as an experimental model by means of which to gain a deeper understanding of the physiological mechanisms involving neuromotor control and its alterations in human disease.

Although all *Drosophila* muscles (both in larvae and adults) are striated, visceral musculature and heart included, three main types of muscles with different features can be recognized:

1) *Tubular muscles*, which include most of the adult skeletal muscles (i.e. muscles which connect different parts of the exoskeleton), for example the tergal depressor of the trochanter or jump muscle. Cross sections of these muscles show rectangular myofibrils, where 8–12 thin filaments surround each thick filament. Nuclei are located in a central position in the cytoplasm (Bernstein et al., 1993).
2) *The indirect flight muscles or IFMs*, also called "fibrillar" muscles, because individual myofibrils can be individually identified by light microscopy. In these muscles the myofibrils have a circular cross section, separated by large mitochondria, which occupy a volume approximately equal to that of the myofibrils. Thin and thick filaments are organized in a highly ordered double hexagonal array (for a review see (Bernstein et al., 1993; Josephson et al., 2000)).
3) *Supercontractile muscles*, which are found in the viscera including the heart, and also include the larval body wall muscles. Thin and thick filaments in these muscles are arranged in a way similar to that of tubular muscles. The peculiar characteristic of supercontractile muscles is their capability to contract to a length well below 50% of resting length (Osborne, 1967; Goldstein, 1971; Goldstein and Burdette, 1971; Hardie, 1976; Herrel et al., 2001).

At variance of larval neuromuscular junction and adult IFM, which in the last three decades have been extensively analysed from the

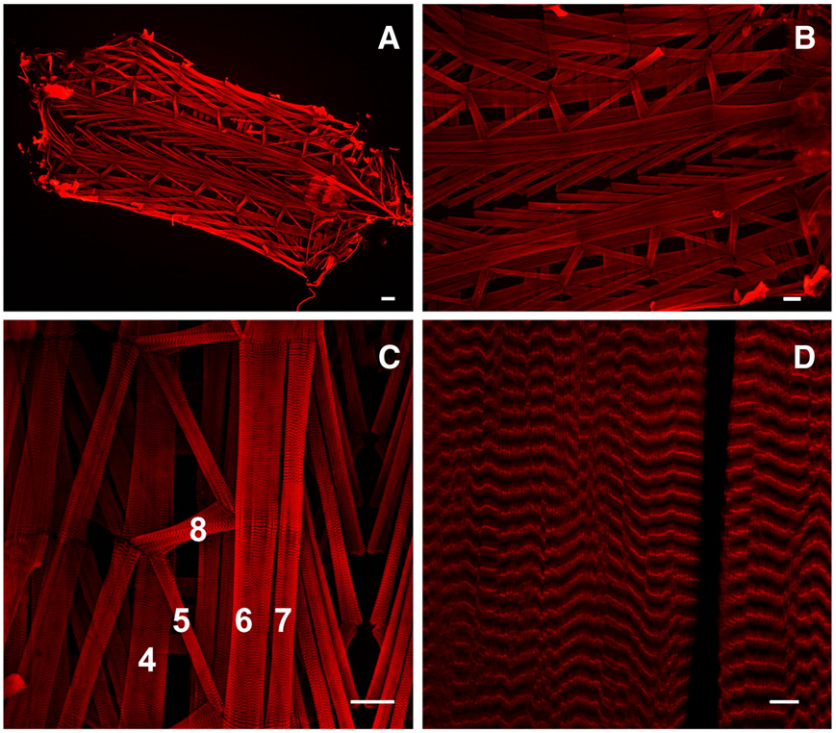

Fig. 1. General organization of body wall segmental muscles in *Drosophila* larva. Muscles are stained with rhodamine–phalloidin. Panel A: body wall muscles of a third instar larva. Calibration bar: 200 μm. B: low magnification picture showing the symmetrical and segmental organization. Calibration bar: 100 μm. Panel C: details of the morphology of the typical muscle pattern present in each segment (numbers identify single muscles). Calibration bar: 100 μm. Panel D: high magnification picture of numbers 6 and 7 longitudinal muscles. Calibration bar: 10 μm.

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