BIOENGINEERING & BIOMEDICAL ENGINEERING RESEARCH SEMINAR

ROLE OF REGULATORY PROTEINS IN THE LATCH-STATE

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ABSTRACT

Smooth muscle (SM) has a unique property, called the latch-state, during which force is maintained for long periods of time at low energy consumption and low myosin activation (phosphorylation) levels. This property has been observed at the whole muscle level. To explain the latch-state, theories extrapolated to molecular mechanisms but they were never verified. One such theory states that, during the cross-bridge cycle, if SM myosin gets dephosphorylated while attached to actin, it will remain attached, in a load-bearing mode. Other theories involve the regulatory proteins (e.g. caldesmon (CaD)) for force maintenance to occur. In an attempt to reproduce the latch-state at the molecular level, we used the in vitro motility assay to measure the velocity (V) of fluorescently labeled actin filaments when propelled by myosin molecules on a coverslip. To this assay, we added a microfluidic chamber to inject myosin light chain phosphatase (MLCP) to efficiently dephosphorylate myosin. A mixture of SM and skeletal (SK) muscle myosin were used, the latter not being regulated by phosphorylation at the muscle level. The rationale behind this protocol was that if the latch-state occurs, we should observe a transient decrease in actin filament V, due to the load induced by the attached, dephosphorylated SM myosin. V would eventually increase to the level of skeletal muscle myosin after the detachment of the latch bridges. For a mixture of [SM] =25 μg/ml/[SK] =80 μg/ml, we observed a constantly increasing velocity profile. Adding CaD, resulted in a complete stop of filaments from 400 to 800 s, after which the motility recovered. These results suggest that CaD is a crucial player to obtain a transient, load bearing phase. Funded by NSERC.

DISCRIMINATING BETWEEN SCHIZOPHRENIA SUBTYPES USING CLUSTERING AND SUPERVISED LEARNING

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ABSTRACT

Schizophrenia (SZ) is a complex neuropsychiatric disorder affecting roughly 1% of the population, making it a significant public health concern [1]. Presentation of SZ includes positive (hallucinations, delusions) and negative (lack of motivation, inability to feel pleasure) symptoms, in addition to cognitive impairments [2]. However, both symptom burden and associated brain alterations are highly heterogeneous and intimately linked to prognosis. To characterize the clinical heterogeneities, there is a need to develop methods that can predict symptom burden at the individual level. To serve this purpose, machine learning algorithms were implemented to first derive clinical subgroups from high-dimensional interrelated clinical information, and then subject-level classification was performed based on magnetic resonance imaging (MRI) derived neuroanatomical measures. Unsupervised hierarchical clustering was performed on the symptom severity data of ~100 SZ patients. The 3-cluster solutions was chosen, following a stability analysis, representing patients with (1) high loads of both negative and positive symptoms, (2) mild-symptomology, or (3) predominantly positive symptoms. Demographic variables and the average cortical thickness in 78 brain regions defined by the Automated Anatomical Labeling atlas parcellation were used as input features into three machine learning algorithms (logistic regression, support vector machine, and random forest), and the 3-cluster solution was used as the class labels. Random forest performance metrics for predicting the group membership of the high-symptomology, and mild-symptomology groups exceeded those of the baseline comparison of the entire SZ population versus normal controls (AUC: 83% and 77% vs. 75%). Overall, the benefit of this study is to provide a means of stratifying SZ patients into homogeneous clinical subgroups that can be predicted using quantifiable, neuroanatomical features; for a future goal of developing methods that can identify individuals at high-risk for conversion to a first episode of psychosis.

1. Sawa et al., Science 296.5568, 692-695 (2002).
2. Owen et al., P. B. Schizophrenia. Lancet 388, 86–97 (2016).

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