зинового взаимодействия в присутствии мутаций в мышечных белках, связанных с врожденными миопатиями, что показано нами на примере тропомиозина с заменой R90P, встроенного в мышечное волокно. Патологическое действие мутации R90P связано с увеличением АТФазной активности миозина и относительного количества головок миозина, которые находятся в конформации сильного связывания, при моделировании различных стадий цикла гидролиза АТФ (Borovikov et al., 2021). Одним из главных эффектов мутации являлось снижение амплитуды движения головок миозина (или SH1-спирали миозина) в цикле гидролиза АТФ. Добавление BDM к мышечным волокнам, содержащим мутантный тропомиозин, частично нормализовало конформационные перестройки миозина, нарушенные в присутствии мутантного тропомиозина, позволяя головкам миозина эффективнее переходить между конформациями слабого и сильного связывания с актином. Из данных следует, что BDM может быть использован для восстановления нормальной регуляции взаимодействия миозина с актином и должен быть протестирован в дальнейшем на других модельных системах и в модельных животных.

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Influence of 2,3-Butanedione-Monoxime on the Interaction of Myosin with Actin in Healthy and in Congenital Myopathy

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Congenital myopathies are a heterogeneous group of human skeletal muscle disorders characterized by muscle hypotonia and weakness. Myopathies have a wide range of clinical phenotypes, which makes it extremely difficult to develop approaches to their treatment. There are several pharmacological agents in clinical use or under clinical investigation for the treatment of cardiomyopathies whose mechanism of action can be used to treat congenital myopathies as well. One such agent is 2,3-butanedione-monoxime (BDM), a noncompetitive inhibitor of myosin ATPase activity used to suppress acute myocardial injury. The molecular mechanisms of inhibition of myosin by BDM in skeletal muscle have not been studied, therefore the aim of this work was to estimate the effect of BDM on the interaction of myosin with actin in the modeling of several ATPase stages in skeletal muscle fiber, in order to assess the prospects for the use of BDM for the treatment of congenital myopathies. We found that BDM enhances the rigidity of myosin binding to actin when modeling weak binding forms of these muscle proteins, which can slow down the transition of actomyosin from the AM · ADP · Pi to the AM · ADP state and is one of the reasons for the decrease in myosin ATPase activity in the presence of BDM. When modeling successive stages of the ATPase cycle using ADP, AMPPNP, ATPγS, and ATP, the myosin heads gradually switch to a state of weak interaction with actin. In the presence of the regulatory proteins tropomyosin and troponin in the muscle fiber, BDM does not affect the formation of a weak form of actomyosin binding, but increases the number of myosin heads essential for force generation. BDM can be used to increase the efficiency of myosin conformational rearrangements in the presence of tropomyosin with the *R90P* mutation associated with congenital myopathy, since this reagent increases the number of myosin heads in the muscle fiber capable of effective conformational rearrangements in the ATPase cycle and partially inhibits the pathological effects of the mutation.

Keywords: actin-myosin interaction, regulation of muscle contraction, muscle fiber, polarized fluorescence, inhibitor of myosin ATPase activity, 2,3-butanedione-monoxime, congenital myopathies