Novel beta subunit mutation causes a slow-channel syndrome by enhancing activation and decreasing the rate of agonist dissociation. [1]

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[2]

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Abstract	We traced the cause of a slow-channel syndrome (SCS) in a patient with progressive muscle weakness, repetitive compound muscle action potential and prolonged low amplitude synaptic currents to a V --> F substitution in the M1 domain of the beta subunit (betaV229F) of the muscle acetylcholine receptor (AChR). In vitro expression studies in Xenopus oocytes indicated that the novel mutation betaV229F expressed normal amounts of AChRs and decreased the ACh EC50 by 10-fold compared to wild type. Kinetic analysis indicated that the mutation displayed prolonged mean open duration and repeated openings during activation. Prolonged openings caused by the betaV229F mutation were due to a reduction in the channel closing rate and an increase in the effective channel opening rate. Repeated openings of the channel during activation were caused by a significant reduction in the agonist dissociation constant. In addition, the betaV229F mutation produced an increase in calcium permeability. The kinetic and permeation studies presented in this work are sufficient to explain the consequences of the betaV229F mutation on the miniature endplate currents and thus are direct evidence that the betaV229F mutation is responsible for compromising the safety margin of neuromuscular transmission in the patient.
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