Subtype-specific Role of Presynaptic K+ Channels in Regulating Transmitter Release

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K^+ channels are powerful regulator for cytosolic Ca^{2+} level both at resting state and during action potentials (APs). Given that neurotransmitter release is highly dependent on presynaptic Ca^{2+} levels, it is crucial to understand how K^+ channels contribute to the regulation of release. It is generally believed that presynaptic K^+ channels regulate spontaneous release and AP-evoked release by regulating resting membrane potential (RMP) and AP duration (APD), respectively, but direct experimental evidence is lacking. Furthermore, it remains to be elucidated whether different K^+ channels use common mechanisms to regulate transmitter release. To investigate these issues, we used blockers for three different types of K^+ channels, M-type (K_V7), D-type (K_V1), and high-voltage activated K_V3 channels, and examined their effects on electrical properties (RMP and APD) and synaptic currents (mEPSC and eEPSC for spontaneous and evoked glutamate release, respectively) in hippocampal excitatory autapses. Blockade of K_V7 and K_V1 depolarized the RMP by 2.3 and 3.4 mV, respectively, while increasing the mEPSC frequency by 1.7 and 1.6 folds, respectively. Their effects on mEPSC frequency were greater than the effect expected from RMP depolarization, which was a 1.4-fold increase by 10 mV when depolarization was induced by current injection. Blockade of K_V3 had no effect on RMP or mEPSC frequency. Blockade of K_V7, K_V1, and K_V3 increased APD by 1.1, 1.1, and 1.4 fold, respectively, while increasing the eEPSC amplitude by 1.4, 1.7, and 1.5 fold, respectively, showing that their effects on eEPSC amplitude and APD are not proportional. Interestingly, 10 mM EGTA in the pipette solution selectively abolished the effects of K_V7, not K_V1 or K_V3, blockade on the glutamate release without affecting the effects on RMP or APD. Furthermore, the effects of K_V7 blockade were completely abolished when L-type Ca^{2+} channels (LTCCs) and calmodulin (CaM) were inhibited, suggesting that K_V7 may regulate LTCC activities and thus Ca^{2+}/CaM activation. On the other hand, the effects of K_V1 blockade on mEPSCs and eEPSCs were completely abolished when phospholipase C (PLC) was inhibited, suggesting the K_V1-depedent regulation of PLC that may facilitate vesicle priming. The effects of K_V3 blockade were not affected either by CaM inhibition or by PLC inhibition, suggesting that increased Ca^{2+} influx by K_V3 blockade facilitates the release directly. Taken together, our study shows that different K^+ channels regulate glutamate release through different mechanisms..