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The Calcium-Sensing Receptor: A Novel Endocannabinoid Receptor

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Abstract

Endogenous cannabinoids, such as anandamide (AEA), have multiple important functions in the brain including modulation of the reward response and neuroplasticity. There are numerous identified and unidentified target receptors for AEA in the nervous system. We have previously determined the calcium-sensing receptor (CaSR), a G-protein coupled receptor, is present at the vast majority of nerve terminals and that it stimulates spontaneous release of glutamate. Preliminary experiments indicate that AEA is an allosteric agonist at the CaSR. Thus, we hypothesized that AEA stimulates spontaneous release via the CaSR. We examined the action of AEA (10 µM) on miniature excitatory post synaptic currents (mEPSCs) recorded in neocortical neurons in tetrodotoxin (TTX, 1 µM) and gabazine (10 µM), voltage-clamped at -70 mV after 14-36 days in culture. AEA strongly increased mEPSC by 15-fold compared with vehicle control after 10 minutes (P=0.005). However, in age-matched neurons isolated from CaSR-deficient (KO) mice, there was substantial attenuation of the response to AEA. Specifically, the rate of increase following AEA application was delayed by 4.3 min (time to 50% maximum value). This was confirmed by comparing the integration of average mEPSC frequency following AEA application, which was reduced by 55% in the CaSR KO neurons (n= 15 and 7 for wild-type and KO respectively; P = 0.0003, Kolmogorov-Smirnov test). Our findings indicate the CaSR mediates the rapid increase of spontaneous glutamate release by AEA but that AEA can still slowly trigger spontaneous release in the absence of the CaSR. These data support the hypothesis that the CaSR is an endocannabinoid receptor.

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