Deciphering the antidepressant effect of ketamine by evaluating its action on astrocytes

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Ketamine (KM), an anaesthetic and psychotomimetic drug, exerts rapid potent and long-lasting antidepressant effect. The cellular and molecular mechanisms of this action are incompletely understood. Besides neurons, KM also affects the function of astroglia. We therefore examined the effect of (sub)anaesthetic doses of KM on fusion pore activity of secretory vesicles, mobility of vesicles carrying the inward rectifying potassium channel (Kir4.1) and stimulus-evoked calcium signaling in cultured rat astrocytes. High-resolution patch-clamp membrane capacitance measurements were used to determine the fusion pore activity of secretory vesicles. The spontaneous mobility and plasmalemmal localization of Kir4.1-EGFP in pKir4.1-EGFP-transfected astrocytes, labeled by the membrane styril dye FM4-64, was determined by confocal microscopy. The effect of KM on ATP-evoked calcium (Ca^{2+}) response was examined by measuring the Fluo-4 fluorescence in KM-treated and non-treated astrocytes. KM-evoked increase in vesicle bursting activity was well correlated with a decrease in irreversible vesicle fission from the plasmalemma (R = 0.93 for increasing KM incubation time and R = 0.99 for increasing [KM]). 30 min KM treatment sufficed to decrease the directional mobility of Kir4.1-positive vesicles. The apparent surface localization of Kir4.1 at astrocyte plasmalemma decreased from 56% in non-treated controls to 43% ($P < 0.05$) and 33% ($P < 0.05$) in astrocytes treated with 2.5 and 25 μM KM, respectively. The ATP-evoked peak Ca^{2+} responses were diminished in KM-treated astrocytes with ATP mobilizing ~3.3-fold less Ca^{2+} than in non-treated controls ($P < 0.001$). Distinct but not mutually exclusive mechanisms of KM action may synergistically evoke changes in synaptic functional plasticity, resulting in sustained strengthening of excitatory synapses, required for antidepressant effects.

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