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Autore	M. Gabrielli
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Sommario

Endocannabinoids (eCBs) are bioactive lipids which primarily influence synaptic communication within the nervous system. They are synthesized by neurons but also by microglia, especially under neuroinflammatory conditions. To exert their function, eCBs travel across the intercellular space. However, how eCBs move extracellularly remains obscure. Our recent evidence indicates that reactive microglia release extracellular vesicles (EVs), which may represent an ideal vehicle for the transport of hydrophobic eCBs. Hence, in this study we investigated whether microglial EVs carry eCBs and may influence neurotransmission. First we analyzed the eCB content of EVs and found a clear enrichment of N-arachidonoylethanolamine (AEA) in EVs relative to parental microglia. This analysis revealed higher AEA levels in EVs shed from the plasma membrane (microvesicles), compared to those which originate from the endocytic compartment (exosomes). To bioassay the activity of vesicular AEA, we used patch clamp analysis of miniature inhibitory post-synaptic currents (mIPSC) on rat hippocampal primary culture. Exposure of neurons to microvesicles (MVs) induced a significant decrease in mIPSC frequency, mimicking the well-known inhibitory action of CB1 receptor agonists. The

	involvement of vesicular AEA in this phenomenon was inferred from the ability of the CB1 receptor antagonist SR141716A to block the reduction of mIPSC frequency evoked by MVs. Western blot analysis showed an increase in ERK phosphorylation in neurons exposed to MVs, which was completely inhibited by SR141716A. This indicate that CB1 receptors activation by AEA-storing MVs translates into downstream signaling. Finally, the use of biotin-AEA revealed an affinity of AEA for MV membrane, indicating that AEA travels in association with MVs surface. Consistent with a surface localization of AEA, MV membranes maintain their capability to decrease mIPSC frequency. Overall, this study shows that microglial MVs carry AEA on their surface to stimulate CB1 receptors on target GABAergic neurons and demonstrates that extracellular vesicular transport of eCBs play a crucial role in the modulation of inhibitory transmission.
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