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Royal jelly-induced neurite outgrowth from rat pheochromocytoma PC12 cells requires integrin signal independent of activation of extracellular signalregulated kinases

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ABSTRACT

We showed earlier that neurite outgrowth of rat pheochromocytoma PC12 cells was stimulated by royal jelly extract (PERJ) or its unique component, AMP N_1-oxide, via adenosine A2a receptors. In this study, we found that stimulated neurite outgrowth occurred in medium supplemented with serum, but not in serum-free medium. The pentapeptide GRGDS, which includes the RGD sequence commonly shared by extracellular matrix (ECM) components, could attenuate the effect of serum, suggesting that integrin receptor signaling was essential for the neurite outgrowth induced by PERJ or AMP N_1-oxide. PERJ or AMP N_1-oxide also activated extracellular signal-regulated kinases 1 or 2 (ERK1/2); however, this activation was not associated with the neurite outgrowth. As it is known that Mn^{2+} induces neurite outgrowth from PC12 cells and activates ERK1/2 through integrin signals and that activation of ERK1/2 is essential for Mn2+-induced neurite outgrowth, a difference in the mechanism between Mn^{2+}-induced and PERJ- or AMP N_1-oxide-induced neurite outgrowth is suggested. Furthermore, we demonstrated that PERJ contained no ECM component-like substances. These results demonstrate that AMP N_1-oxide and its analogues were the only entities in PERJ with neurite outgrowth-inducing activity and that they required integrin signaling in addition to activation of A2a receptors to induce neurite

outgrowth.

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