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Epinephrine Induces Neuronal Differentiation of alpha 2 Adrenergic Receptor-Transfected PC 12 Cells

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AIM

Despite considerable progress in dissecting the physiological roles of α_2-adrenergic receptor (α_2-AR) subtypes, the intracellular biochemical mechanism(s) mediating the physiological functions of α_2-ARs remain largely unknown. In this study we have used PC 12 cells, a clonal rat pheochromocytoma cell line, which, in response to chronic treatment with Nerve Growth Factor (NGF), differentiate to sympathetic-like neurons. Our objective was to understand the signal transduction mechanisms from stimulated α_2-AR by correlating the effect of adrenergic agonists to the differentiating action of NGF and its signaling mechanisms.

MATERIALS AND METHODS

PC 12 cells expressing stably human adrenergic receptor cDNAs, coding for α_{2A}, α_{2B} and α_{2C} subtypes, were cultured in collagen-coated dishes in high glucose DMEM supplemented with 10% horse serum, 5% FBS, in the presence of antibiotics. Differentiation was induced by treatment with NGF or Epinephrine for 4 days. Duplicate blots prepared from cell lysates were incubated with anti-P-MAPK antibody and immunostained proteins were visualized with ECL detection system. Activation of AP-1 was studied by gel mobility shift assay with cell extracts prepared from PC 12 transfectants, as previously described.

RESULTS

Application of epinephrine to α_{2C}-PC 12 cells induced morphological changes similar to those seen after application of NGF. This effect was inhibited by treatment with the α_2-specific Antagonist Yohimbine or the MEK 1 inhibitor PD 98509. No morphological change was seen in α_{2A}-PC 12 after exposure to epinephrine, implying that the differentiating effect is subtype-specific. In addition, epinephrine caused a rapid activation of p42/p44 MAPK in both α_{2A}-PC 12 and α_{2C}-PC 12 transfectants and, later on, a parallel increase in the AP-1 DNA binding activity. Application of epinephrine for 4 days increase the level of peripherin expression, a cytoskeletal protein expressed in neuronal cells, and this augmentation was considerably diminished in the presence of RX821002 antagonist.

CONCLUSIONS

Epinephrine induces neuronal differentiation, both morphologically and biochemically, of PC12 cells transfected with α_2-AR subtypes. This differentiating action is mediated, like the one induced by NGF, by p42/p44 MAPK and eventuates to AP-1 activation to the nucleus. These findings suggest that epinephrine may act as a neuronal differentiating agent in vivo.