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论著

阿托伐他汀通过激活PI3K/Akt/mTOR信号转导而促进神经元突起生长

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摘要 目的 探讨阿托伐他汀(Ato)对体外培养大鼠皮质神经元突起生长促进作用的信号转导机制。方法 取培养7 d大脑皮质神经元, 分为Ato 10 μmol·L^{-1}作用48 h组和阻断剂+Ato组, 先分别加入阻断剂PD98059 50 μmol·L^{-1}、LY294002 30 μmol·L^{-1}、曲西立滨(TCBN)2.5 μmol·L^{-1}和西罗莫司(雷帕霉素, Rapa) 100 nmol·L^{-1}作用1 h, 再加入Ato共同作用48 h。应用倒置相差显微镜观察神经元突起生长状况;Western 印迹法检测磷酸化的磷酸肌醇依赖激酶1(PDK1)、磷酸化蛋白激酶B(Akt)、磷酸化西罗莫司靶蛋白(mTOR)、磷酸化的核糖体S6激酶(p70S6K)和磷酸化的真核翻译起始因子4E结合蛋白 1(p-4E-BP1)的表达。结果 形态学观察结果显示, Ato 10 μmol·L^{-1}组可明显促进突起生长, 表现为突起总长度增加、一级突起数目增多、末端分支数增多及胞体面积增大。PD98059, LY294002, TCBN和Rapa均可阻断Ato对神经元突起生长的促进作用。Western印迹结果显示, Ato 10 μmol·L^{-1}可显著上调p-PDK1, p-Akt(Ser473), p-mTOR, p-p70S6K和p-4E-BP1蛋白表达水平(P<0.01)。LY294002可显著阻断Ato引起的p-PDK1, p-Akt(Ser473) 蛋白表达水平增加(P<0.01)。TCBN 可显著阻断Ato引起的p-mTOR蛋白表达水平增加(P<0.01)。Rapa可明显阻断Ato引起的p-p70S6K和p-4E-BP1蛋白表达水平增加(P<0.01)。结论 Ato对体外培养皮质神经元突起发育的促进作用可能与激动MEK/ERK信号转导通路有一定的关系, 主要可能与通过激活PI3K/Akt/mTOR信号转导通路有关。

关键词 阿托伐他汀 皮质神经元 突起生长 信号转导通路 磷酸酰肌醇-3激酶 蛋白激酶B 哺乳动物雷帕霉素靶蛋白
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Atorvastatin promotes neurite growth by activating PI3K/Akt/mTOR signal transduction

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Abstract

OBJECTIVE To discuss the signal transduction mechanism of facilitation of atorvastatin (Ato) on the rat cortical neurite outgrowth *in vitro*. **METHODS** Cerebral cortical neurons on the 7 d after incubation were selected and treated with Ato 10 μmol·L^{-1} for 48 h in one group while blocker + Ato group was treated with PD98059 50 μmol·L^{-1}, LY294002 30 μmol·L^{-1}, triciribine (TCBN) 2.5 μmol·L^{-1}, and sirolimus (Rapamycin, Rapa) 100 nmol·L^{-1} added 1 h prior to Ato, and coincubated for 48 h. The growth of neurites was observed under an inverted phase contrast microscope. The protein expressions of phosphorylated phosphoinositide-dependent kinase1 (PDK1), phosphorylated protein kinase B (Akt), phosphorylated mammalian target of sirolimus(Rapamycin, mTOR), phosphorylated ribosomal S6 kinase (p70S6K) and phosphorylated eukaryotic translation initiation factor binding protein 1 (4E-BP1) were detected by Western blotting. **RESULTS** The morphological results showed that the growth of neurites in Ato 10 μmol·L^{-1} group was significantly promoted, as was evidenced by the increase in the total length of neurites, number of primary neurites and terminal branches, and by the enlarged area of somatic cells. PD98059, LY294002, TCBN and Rapa could stop Ato from facilitating the neurite outgrowth. Results of Western blotting showed that Ato 10 μmol·L^{-1} could significantly increase the protein expression level of p-PDK1, p-Akt(Ser473), p-mTOR, p-p70S6K and p-4E-BP1. LY294002 could significantly block the increase in protein expression levels of p-PDK1 and p-Akt (Ser473) which were caused by Ato (P<0.01). TCBN could significantly block the increase in protein expression level of p-mTOR caused by Ato (P<0.01). Rapa could significantly block the increase in protein expression level of p-p70S6K and p-4E-BP1 (P<0.01). **CONCLUSION** Facilitation of Ato on rat cortical neurite outgrowth *in vitro* is possibly related to the activated MEK/ERK signal transduction pathway, especially to the activated PI3K/Akt/mTOR signal transduction pathway.

Key words atorvastatin cortical neurons neurite outgrowth signal transducition pathways

phosphoinositide-3 kinase protein kinase B mammalian target of Rapamycin

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