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阿尔茨海默病小鼠脑中p75神经营养因子受体和老年斑的表达

到：

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Title: Expression profile of p75NTR and senile plaque formation in brain of AD transgenic mice

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摘要: 目的 探讨阿尔茨海默病（alzheimer’s disease，AD）中p75神经营养因子受体（p75 neurotrophin receptor，p75NTR）表达和老年斑形成的时相关系及变化情况。 方法 取3、6、9月龄雄性B6C3-Tg(APPSwePSEN1dE9)85Dbo/J转基因小鼠及同窝雄性野生型小鼠脑组织，采用刚果红、免疫组化和荧光染色方法观察脑片中老年斑和变性p75NTR阳性神经纤维的表达以及共定位情况，并分别通过ELISA、Western blot方法检测脑匀浆中总β淀粉样蛋白（amyloid-β，Aβ）和p75NTR蛋白水平。 结果 转基因小鼠3月龄时皮层、海马未见老年斑形成，6月龄时皮层和海马可见到少量老年斑形成，在9月龄时此处老年斑沉积明显增多。ELISA检测结果提示Aβ水平随小鼠月龄增加而增多。与同龄野生型小鼠相比，3月龄转基因小鼠皮层和海马可见p75NTR阳性神经纤维增多，且部分神经纤维末梢变性膨大；6月龄者皮层、海马p75NTR阳性神经纤维增多，出现部分呈不规则球形的变性神经末梢；9月龄者皮层、海马p75NTR变性神经末梢显著增多。野生型小鼠在各年龄段均未见变性的p75NTR阳性神经末梢。Western blot结果表明转基因和野生型小鼠脑内p75NTR水平均随着年龄增加而增加，且同月龄间相比前者高于后者（$P<0.01$）。共聚焦显微镜观察到p75NTR阳性的变性神经末梢位于老年斑中心部位，而不表达p75NTR的变性神经末梢位于老年斑外周。 结论 在转基因小鼠脑内Aβ能增加p75NTR的表达；p75NTR阳性神经纤维早于老年斑出现，且在老年斑形成后位置靠近老年斑中心，提示其促进了Aβ沉积的起始过程。

Abstract: Objective To compare the expression profile of p75 neurotrophin receptor (p75NTR) and senile plaque formation in a mouse model of Alzheimer's disease (AD). Methods Brain sections and homogenates from male B6C3-Tg (APPSwePSEN1dE9) 85Dbo/J transgenic mice and their male wild type littermates aged 3, 6, or 9 months old (*n*=6 for each age) were subjected in this study. The senile plaques, degenerated p75NTR positive neurites and their colocalization were illustrated using Congo red, immunohistochemical and fluorescence staining. ELISA and Western blot analysis were applied to detect the expression level of total Aβ and p75NTR in brain homogenates. Confocal microscopy was used to observe the special distribution of senile plaque, p75NTR positive and negative degenerated neurites. Results In the brain of AD transgenic mice, the senile plaques appeared firstly at 6 months in the cortex and hippocampus, where the burden of senile plaques increased at 9 months. It showed an age-dependent increase of Aβ in both Congo red staining and ELISA measures. Meanwhile, the onset of degenerated p75NTR positive neurites occurred as early as 3 months when senile plaques were not yet formed, mainly in the cortex and hippocampus. The expression of p75NTR was elevated with the increase of age in both AD transgenic mice and their wild type littermates, which was even higher in transgenic mice. Confocal microscopy showed that p75NTR positive degenerated neurites located in the center of senile plaques while p75NTR negative degenerated neurites were at the periphery of the plaques. Conclusion p75NTR expression increases with aging, and is further activated by Aβ. The degenerated p75NTR positive neurites appear much earlier in the cortex and hippocampus than the formation of Aβ plaques, suggesting that p75NTR may promote the initiation of senile plaque formation.

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