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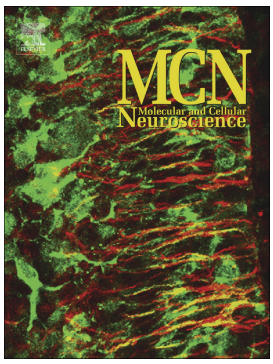

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A small peptide derived from BMP-9 can increase the effect of bFGF and NGF on SH-SY5Y cells differentiation

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Abstract

The current aging of the world population will increase the number of people suffering from brain degenerative diseases such as Alzheimer's disease (AD). There are evidence showing that the use of growth factors such as BMP-9 could restored cognitive function as it acts on many AD hallmarks at the same time. However, BMP-9 is a big protein expensive to produce that can hardly access the central nervous system. We have therefore developed a small peptide, SpBMP-9, derived from the knuckle epitope of BMP-9 and showed its therapeutic potential in a previous study. Since it is known that the native protein, BMP-9, can act in synergy with other growth factors in the context of AD, here we study the potential synergistic effect of various combinations of SpBMP-9 with bFGF, EGF, IGF-2 or NGF on the cholinergic differentiation of human neuroblastoma cells SH-SY5Y. We found that, in opposition to IGF-2 or EGF, the combination of SpBMP-9 with bFGF or NGF can stimulate to a greater extent the neurite outgrowth and neuronal differentiation toward the cholinergic phenotype as shown by expression and localization of the neuronal markers NSE and VAchT and the staining of intracellular calcium. Those results strongly suggest that SpBMP-9 plus NGF or bFGF are promising therapeutic combinations against AD that required further attention.

1. Introduction

The current aging of the world population will increase the incidence of neurodegenerative disorders such as Alzheimer's disease (AD), thus creating a huge socio-economic burden estimated to be over several hundreds of billions of US dollars (Alzheimer's Association, 2017; World Health Organization, 2017). AD is characterized by three major hallmarks: (1) dysfunctional cholinergic system (Geula et al., 2008), (2) senile plaque accumulation made of toxic β–amyloid peptide aggregates (Murphy and LeVine 3rd, 2010) and (3) the hyperphosphorylation of Tau protein, resulting in neurofibrillar entanglements (Alonso et al., 1996; Augustinack et al., 2002).The current treatments found on the market such as rivastigmine, galantamine, donepezil, or memantine cannot stop the evolution of the disease (Giacobini and Gold, 2013; Hansen et al., 2008; Tricco et al., 2013). Yet, there is no known cure of AD.

It has been shown that the use of growth factors, normally found in the healthy brain, but dysregulated in AD patients, could have a promising therapeutic potential (Lauzon et al., 2015). Among the growth factors, Bone Morphogenetic Protein-9 (BMP-9), a member of the TGF-β superfamily, was shown to act simultaneously on several hallmarks of the disease (Burke et al., 2013; Lopez-Coviella et al., 2002, 2000; Schnitzler et al., 2010). For instance, it has been shown that BMP-9 could reduce the accumulation of senile plaque within the APP/PS1 mouse brain and restore the cholinergic function (Burke et al., 2013). It was also demonstrated that BMP-9 can induce the neuronal differentiation toward