論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	AHMED KHALID MOHAMED ALBASHIR AHMED
論文題名 Title	The effects of Bone Morphogenetic Protein 4 on adult neural stem cell proliferation, differentiation and survival in an *in vitro* model of ischemic stroke (Bone morphogenetic protein 4がin vitro虚血モデル下における神経幹細胞の増殖、分化および生存率に及ぼす影響)

論文内容の要旨

〔目　的(Purpose)〕

The subventricular zone (SVZ) of the lateral ventricles represents a main region where neural stem cells (NSCs) of the mature central nervous system (CNS) reside. The adult NSCs exhibit the potential to proliferate and differentiate into other neural cells, such as neurons and astrocytes. Bone morphogenetic proteins (BMPs) are the largest subclass of the transforming growth factor-β (TGF-β) superfamily of ligands. BMP4 is a member of this family and plays important roles in CNS development and adult NSC differentiation. Furthermore, BMP4 expression levels are upregulated in CNS diseases as spinal cord injury and neonatal hypoxic-ischemia. However, the exact effects of BMP4 on SVZ adult NSCs in CNS ischemia are still unclear. I examined the behavior of adult NSCs under *in vitro* ischemic insults and explored the effects of BMP4 treatment on their responses.

〔方法ならびに成績(Methods/Results)〕

The SVZs of adult mice brains were isolated to obtain NSCs. Cultured NSCs were examined for their survival, proliferation and differentiation potential under normoxic (normal oxygen and glucose conditions) and ischemic conditions. Oxygen and glucose deprivation (OGD) were used as an *in vitro* model of ischemia. NSCs characteristics were further examined with BMP4 treatment in both normoxic and OGD conditions.

In contrast to normoxic and hypoxic conditions, I observed that anoxia resulted in reduced viability of adult NSCs, and that BMP4 treatment clearly rescued apoptotic cell death following anoxia.

Furthermore, BMP4 treatment exhibited a strong inhibitory effect on cellular proliferation of the adult NSCs in normoxic conditions. Moreover, such inhibitory effects of BMP4 treatment were also found in OGD conditions, despite the enhanced cellular proliferation of the adult NSCs that was observed under such ischemic conditions.

I further investigated adult NSCs differentiation response in similar conditions. Increased neuronal and astroglial commitment of adult NSCs were found in the OGD conditions, whereas a reduction in differentiated neurons and an increase in differentiated astrocytes were observed following BMP4 treatment.

Evaluation of *Id* genes family revealed changes in their expression levels under OGD conditions with and without BMP4 treatment.

〔総　括(Conclusion)〕

I examined the effects of oxygen and glucose deprivation (OGD) and/or BMP4 treatment on NSCs characteristics *in vitro*. The present study indicates that BMP4 modulates proliferation and differentiation of SVZ-derived adult NSCs and promotes cellular survival in the *in vitro* model of ischemic stroke.

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論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本研究は、成体脳室下帯由来の神経幹細胞の増殖・分化能および細胞死に対するBMP4の作用をin vitro虚血モデルを用いて検討を行った。無酸素状態により神経幹細胞の生存率は著しく低下したが、BMP4投与によりその細胞死が有意に改善することが明らかとなった。成体神経幹細胞の増殖能は、虚血状態において促進されるがその効果はBMP4によって著しく抑制された。また、コントロール条件下においても同様にBMP4によって増殖能は有意に低下することが明らかとなった。BMP4が神経幹細胞の分化能に及ぼす影響については、コントロール条件下では神経細胞への分化には変化はみられなかったが、アストロサイトへの分化は有意に促進された。一方、虚血条件下では神経細胞およびアストロサイトへの分化はともに有意に促進されたが、BMP4投与により神経細胞への分化は抑制方向に働き、アストロサイトへの分化はさらに促進方向へ働くことが分かった。本研究成果は、BMP4が虚血下における成体脳室下帯由来の神経幹細胞におよぼす影響を明らかにした重要な成果であり、虚血性脳卒中におけるBMP4治療応用の可能性を示す知見である。それゆえ博士（医学）の学位に値する。