Brain Disorders & Therapy
ISSN: 2168-975X

Romero and Zanini, Brain Disord Ther 2016, 5:1
DOI: 10.4172/2168-975X.1000205

Commentary Open Access

Tyrosine Kinase and Mitogen Activated Protein (MAP) Kinase Pathway on Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage

Flavio Ramalho Romero* and Marco Antônio Zanini

Neurosurgical Division, Department of Neurology and Psychiatry, São Paulo State University (UNESP), Brazil

Abstract

Cerebral vasospasm is a severe complication after an aneurysm rupture. Many efforts have been done to understand the complexity signaling pathways involved in this condition. MAP kinase has been suggested to be one of the most important signaling pathways involved in cerebral vasospasm. This pathway is clinically important as it has both outcome and therapeutic implications.

Keywords: MAP kinase; Tyrosine kinase; Signaling pathways; Cerebral vasospasm

Introduction

Cerebral vasospasm is the most important complication following the subarachnoid hemorrhage (SAH) [1,2]. Despites current medical treatment, including hemodynamic therapy and calcium block channels medicines, up to 15% of surviving patients develops severe complications from vasospasm, making cerebral vasospasm the most important issue in outcome of patients after an aneurysm rupture [1-4]. Cerebral vasospasm involves a complex multiple signaling pathways. Many authors have been identified MAP kinase as the most important signaling pathway on vasospasm regards proliferation, inflammation, cell death, smooth muscle phenotype changes, vascular remodeling, and vascular contraction [2-6]. This mini review describes some important point in this pathway and tries to introduce the new molecular specific targets in selective treatment on vasospasm.

Tyrosine Kinase and MAP Kinase

Contraction of cerebral arteries is directly controlled by MAP kinase, involved in Ca^{2+} regulation on cerebral smooth muscle cells. After an aneurysm rupture, hemoglobin, vasoactive agents (endothelin-1) and free radicals of blood clot enhance and activate MAP kinase expression in vascular smooth muscle cells [2,7,8].

Also, fibroblasts compaction is other important pathway involved in cerebral vasospasm. Some authors determined that Tyrosine kinase is responsible for this mechanism, activated by G-protein coupled receptor agonist and growth factors [1,2]. Di Savio et al. founded increased levels of G-protein receptor agonist such as adenosine triphosphate and endothelins, growth factors, and their receptors in cerebrospinal fluid and cerebral arteries in experimental models [7]. Other substrates were described after tyrosine kinase activation, such as Ras protein and phosphatidyl inositol-3 kinase tyrosine kinase. Ras is increased after spasm stimulation, and phospatidyl-inositol-3 kinase is enhanced after vasospasm in animals. In experimental models, sumarin (tyrosine kinase inhibitors) reduced vasospasm. By the other side, this response was not obtained with phosphatidylinositol-3-kinase inhibitors (Figure 1) [2,7].

Conclusion

Pathogenesis of cerebral vasospasm involves multiple signaling pathways in proliferation, in inflammation, cell death, smooth muscle phenotype changes, vascular remodeling, and contraction. Understanding pathways in vasospasm might offer new possibilities for selective treatment of cerebral vasospasm in the future. Additional research is required to clarify the roles of these pathways and agents in vasospasm.

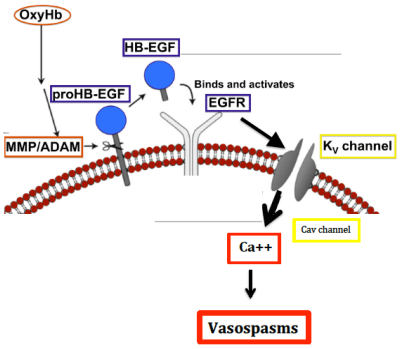

Figure 1: Molecular pathway in cerebral vasospasm, focusing tyrosine kinase and MAP kinase. Growing factors are secreted polypeptides that regulate the growth of normal and pathological cells. There are seven EGF growing factors, including the Heparin Binding EGF-like factor (HB-EGF). Oxyhemoglobin and HB-EGF are booth protagonists in a process of voltage dependent potassium channels supression. Many voltage dependent channels are opened after a membrane depolarization. Oxyhemoglobin activates a metalloprotease (MMP9/ADAM) breaking the membrane protein called pro HB-EGF, activating the transmembrane tyrosine kinase protein EGFR. This pathway decreases the Kv channel expression, creating a natural membrane potential in muscular cells, that induces an increase of Ca^{++} passage through Cav channels resulting in a reduction of vascular caliber (vasospasm).

References

1. Adam LP, Hathaway DR (1993) Identification of mitogen-activated protein kinase phosphorylation sequences in mammalian h-caldesmon. FEBS Lett 322: 56-60.
2. Romero FR, Figueiredo EG, Teixeira MJ (2011) Signaling pathways in cerebral vasospasm. Arq Bras Neurocir 3: 116-119.
3. Bulter WE, Peterson JW, Zervas NT, Morgan KG (1996) Intracellular calcium,

***Corresponding author:** Flavio Ramalho Romero, Neurosurgical Division, Department of Neurology and Psychiatry, Botucatu Medical School, São Paulo State University (UNESP), Botucatu, Brazil, Tel: 551433543594; E-mail: frromero@ig.com.br

Received December 28, 2015; **Accepted** January 19, 2016; **Published** January 23, 2016

Citation: Romero FR, Zanini MA (2016) Tyrosine Kinase and Mitogen Activated Protein (MAP) Kinase Pathway on Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage. Brain Disord Ther 5: 205. doi:10.4172/2168-975X.1000205

myosin light chain phosphorylation, and contractile force in experimental cerebral vasospasm. Neurosurgery 38: 781-787.

4. Cook DA, Vollrath B (1995) Free radicals and intracellular events associated with cerebrovascular spasm. Cardiovasc Res 30: 493-500.
5. Dankbaar JW, Rijsdijk M, Van der Schaaf IC, Velthuis BK, Wermer MJ, et al. (2009) Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neuroradiology 51: 813-819.
6. Dehdashti AR, Mermillod B, Rufenacht DA, Reverdin A, De Tribolet N (2004) Does treatment modality of intracranial ruptured aneurysms influence the incidence of cerebral vasospasm and clinical outcome? Cerebrovasc Dis 17: 53-60.
7. Di Salvo J, Steusloff A, Semenchuk L, Satoh S, Kolquist K, et al. (1993) Tyrosine kinase inhibitors suppress agonist induced contraction in smooth muscle. Biochem Biophys Res Commun 190: 968-974.
8. Dorsch NW (1995) Cerebral arterial spasm: a clinical review. Br J Neurosurg 9: 403-412.