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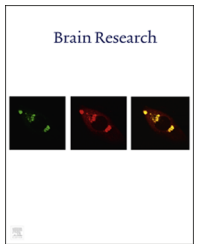

Review

# Endogenous brain protection: What the cerebral transcriptome teaches us

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ABSTRACT

Despite efforts to reduce mortality caused by stroke and perinatal asphyxia, these are still the 2nd largest cause of death worldwide in the age groups they affect. Furthermore, survivors of cerebral hypoxia-ischemia often suffer neurological morbidities. A better understanding of pathophysiological mechanisms in focal and global brain ischemia will contribute to the development of tailored therapeutic strategies. Similarly, insight into molecular pathways involved in preconditioning-induced brain protection will provide possibilities for future treatment.

Microarray technology is a great tool for investigating large scale gene expression, and has been used in many experimental studies of cerebral ischemia and preconditioning to unravel molecular (patho-) physiology. However, the amount of data across microarray studies can be daunting and hard to interpret which is why we aim to provide a clear overview of available data in experimental rodent models. Findings for both injurious ischemia and preconditioning are reviewed under separate subtopics such as cellular stress, inflammation, cytoskeleton and cell signaling. Finally, we investigated the transcriptome signature of brain protection across preconditioning studies in search of transcripts that were expressed similarly across studies. Strikingly, when comparing genes discovered by single-gene analysis we observed only 15 genes present in two studies or more. We subjected these 15 transcripts to DAVID Annotation Clustering analysis to derive their shared biological meaning. Interestingly, the MAPK signaling pathway and more specifically the ERK1/2 pathway geared toward cell survival/proliferation was significantly

Abbreviations: MCAO, middle cerebral artery occlusion; ECA, external carotid artery; CCAO, common carotid artery occlusion; BCAO, bilateral common carotid occlusion; DHT, dihydrotestosterone

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enriched. To conclude, we advocate incorporating pathway analysis into all microarray data analysis in order to improve the detection of similarities between independently derived datasets.



## Contents



## 1. Introduction

Hypoxic-ischemic brain injury is still a major cause of death in both neonates and adults worldwide. Despite efforts in the last decade to reduce mortality caused by stroke it remains the 2nd largest cause of death worldwide, and in 2011 stroke was responsible for 6.2 million adult deaths. The yearly number of deaths caused by stroke has even grown with 600,000 since the year 2000 (World Health Organization, 2011). In addition, survivors often suffer significant neurological disabilities (Kelly-Hayes et al., 2003; Mukherjee and Patil, 2011).

Perinatal asphyxia is a different type of hypoxic-ischemic brain injury affecting neonates. It is the 2nd largest cause of death among neonates and causes over 20% of neonatal deaths (World Health Organization, 2010). Survivors of perinatal asphyxia are at risk of developing hypoxic-ischemic encephalopathy, which often leads to permanent neurological disabilities such as cerebral palsy (Perez et al., 2013).

Both stroke and perinatal asphyxia have high mortality and high neurological morbidity in the age groups they affect. Although these conditions differ in etiology, for example stroke is a local hypoxic-ischemic event whereas perinatal asphyxia is a global hypoxic-ischemic event; it is likely that there are some common denominators in the mechanism of injury.

In order to limit mortality and neurological morbidities caused by hypoxic-ischemic brain damage we need a better understanding of the injurious mechanisms. Understanding the molecular pathophysiology of hypoxia-ischemia in the brain will provide possibilities for future therapeutic strategies. Several different rodent models have been developed to study the pathophysiology of both focal and global ischemia.