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Brain 11: What's new in stroke research?

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Abstract

The International Society of Cerebral Blood Flow and Metabolism promotes research centering on furthering the understanding of neurological conditions that result from ischemia and related injuries. This past meeting (Brain 11) focused on state of the art research which shed light on the pathophysiology of these conditions as they pertained to the cerebral vasculature including the blood brain barrier and angiogenesis, immune mechanisms, regeneration and repair following such insults. The meeting also covered a variety of potential therapeutic strategies ranging from cell based therapy, induced tolerance and targeting of specific immune or cell death pathways. There was also focus on how the peripheral circulation contributes to such brain injury.

Keywords

cerebral ischemia; stem cells; inflammation; neuroprotection; neurogenesis; neurovascular unit

Meeting details:

Brain 11 is the 25th International Symposium on Cerebral Blood Flow, Metabolism and Function, and was organized by Anna Planas of IDIBAPS and colleagues on behalf of the International Society for Cerebral Blood Flow and Metabolism (ISCBFM). ISCBFM is an organization of scientists and physicians interested in the study of cerebral blood flow and metabolism whose members come from all over the world. This meeting is held biennially, and attracts over 1,000 scientists and physician scientists from 40 different countries. The program included state-of-the-art topics such as neurovascular biology, cell based therapy, neuroimmunology and neuroimaging.

Neuron-blood vessel interactions

The meeting began with a plenary lecture given by Dr. B. V. Zlokovic of the University of Rochester (USA) who presented work demonstrating a previously unrecognized role of the cerebral vasculature and neurodegeneration with an emphasis on pericytes. The role of

pericytes in the brain vasculature has only recently been shown to contribute significantly to neurovascular functions. By studying mice deficient in pericytes, Dr. Zlokovic and colleagues found that this led to disruption of the blood brain barrier (BBB) with subsequent leakage of blood derived neurotoxins [1]. Entry of neurotoxins then led to neurodegeneration. These findings have important clinical implications because they suggest the importance of targeting the brain vasculature in the prevention of neurodegenerative disease.

The link between Alzheimer's disease and inflammation is often controversial, but lipopolysaccharide (LPS) induced inflammation appears to prevent the normal efflux of beta amyloid out of the brain, potentially leading to abnormal retention and accumulation.

Inflammation is known to negatively affect BBB integrity. Thus, anti-inflammatory strategies could be neuroprotective by virtue of their salutary effects on the brain vasculature. Cannabinoids are known to be neuroprotective, and one mechanism of protection appears to be through anti-inflammatory properties [2]. LPS treatment increased cannabinoid receptor (CB2) expression, and CB2 agonists increased TJP expression and strengthened the BBB while preventing leukocyte adhesion. This would suggest that a potential protective mechanism of cannabinoids is through an anti-inflammatory, BBB strengthening property.

Factors leading to BBB disruption were also discussed in other presentations. While past work has demonstrated the importance of matrix metalloproteinase (MMP) activation in BBB disruption, repair mechanisms were explored as well [3]. While tight junction proteins (TJPs) disappear early after ischemic stroke, they reappear at 3 weeks in newborn vessels and even surrounding pericytes and astrocytes, and this was correlated to increased MMP-2 (astrocytes) and MMP-3 (pericytes). These observations suggest that MMPs, while acutely damaging to the BBB, may also be important in angiogenesis and BBB remodeling.

Restorative therapies:

With the recognition that most patients do not present for medical attention until hours or sometimes days following stroke, efforts to understand how the brain recovers from cerebral ischemic insults and to identify potential therapeutic strategies have been the focus of this field for nearly a decade. With recent interest in the potential of stem cells to cure a variety of diseases, its application in brain ischemia is no exception.

Cell based therapy:

The current status of cell based therapy in stroke and related conditions was reviewed. Both neuron derived and mesenchymal cell derived stem cells could be administered to laboratory animals subjected to various types of central nervous system insults [4] [5]. These cells integrate into the brain and lead to improvement in long term neurological function. Further, co-treatment with trophic factors could further improve the ability of stem cells to repair injury to the spinal cord. Advanced imaging techniques allow non-invasive nanoparticle labeling of the transplanted, and these studies were able to compare the efficiency of

transplantation of mesenchymal bone marrow derived cells (MSCs) when given peripherally or intracerebrally, with more efficient uptake occurring when given intracerebrally.

Human studies of cell based therapies were also reviewed [6]. While the collective clinical experience is still in its infancy, a few anecdotal cases of remarkable functional improvement were shown. Most clinical studies are examining the role of MSCs, and the studies are at the Phase II level, where safety, rather than efficacy are being evaluated. However, it was emphasized that cell based therapy is still in the early stages of investigation and its precise role in the treatment of patients is unclear, yet many speakers seemed optimistic.

Endogenous CNS repair mechanisms and neurogenesis:

Central nervous system (CNS) injury frequently leads to an inevitable and irreversible loss of function because of the widely held notion that neurons, particularly in the adult brain, do not regenerate. However, recent work has shown that neurons are capable of regenerating ('neurogenesis') in certain brain regions and under specific settings. Thus, the possibility that brain cells can be restored through endogenous repair mechanisms opens up a host of therapeutic strategies to optimize this recently recognized property of neurons [7].

In one session, neuroscientists discussed novel applications of neurogenesis through activation of endogenous neural stem cells (NSCs) and/or pharmacological pretreatment of neural stem cells prior to transplantation. Attempts to maximize the spread of neurogenesis after injury have yielded broad insights into the identification of specific molecules with neuroprotective properties. Several researchers presented new strategies for improving CNS repair during various insults. NSCs pretreated with drugs such as minocycline, lipopolysaccharide (LPS) and agmatine (an endogenous inhibitor of nitric oxide synthase) all attenuated infarct size and enhanced neurological recovery when transplanted into ischemic brains of rodents. Minocycline treated NSCs subjected to ischemia-like insults in vitro followed by reperfusion deregulated several antioxidant genes and trophic factors such as Nrf2, NQO1, HO, BDNF, NGF, GDNF and VEGF. A few investigators also suggested that PI3k/Akt or Akt/JNK signaling pathways were associated with this neuroprotection. Preconditioning and other approaches aimed at enhancing NSC protection, such as transfection of transgenes was also presented. Some studies explored the role of microRNA's (miRNA) that could regulate the expression of various genes. In one study, inhibiting miRNA (mir1) which binds to the 3' UTR of the IGF-1 gene could promote protection of NSCs, and lead to improved NSCs for transplantation.

Inflammation in stroke:

The role in inflammation in brain ischemia has been increasingly studied, and generally recognized that the acute inflammatory response negatively affects stroke outcome [8]. Several presentations characterized specific immune targets that could be manipulated to improve outcome from experimental models. Studies of sphingosine kinase antagonists, the P2Y12 nucleotide receptor (and also the site at which the popular anti-platelet drug clopidogrel acts), and agonists of cannabinoids/cannabinoid receptors, all showed salutary effects on brain cell survival and neurological outcome. A few presentations showed that ischemic tolerance, or the phenomenon that sublethal stress leads to protection from a

subsequent lethal insult, can be conferred by manipulating certain inflammatory pathways. These included the stimulation of toll-like receptor 3 (TLR3) or the sphingosine kinase-2. Ischemic preconditioning was also correlated to increases in endogenous anti-inflammatory factors including agmatine.

The role of microglia in brain ischemia was also explored in a symposium that challenged the notion that microglia possess damaging functions in both acute and chronic neurological conditions. While some microglial properties certainly appear to worsen outcome from brain ischemia, ablation of brain microglia in the adult brain led to worsening of ischemic outcome and alteration of the ischemic inflammatory response [9]. This worsening seemed to be related to the depletion of microglia derived prosurvival factors such as IGF-1 and galectin-3. However, the deletion of microglia from the developing brain had no effect on stroke outcome and emphasizes clear differences in responses to ischemic insults in the developing versus adult brain. Other microglial functions appear vital to effective recovery. A newly characterized phagocytic receptor, TREM-2 (triggering receptor expressed on myeloid cells), may be important in the removal of injured neurons, and its deficiency could potentially negatively impact stroke outcome. Examination of microglia in aged human brain samples of subjects carrying a diagnosis of Alzheimer's and related conditions also revealed that during senescence, microglia show signs of degeneration and abnormal responses [10]. Further, microglia show signs of damage prior to the development of tau pathology, and would suggest that treatments targeting microglia are unlikely to affect neurodegeneration in conditions such as Alzheimer's.

Importance of the peripheral circulation.

The peripheral circulation has been understudied in this field, but recent work presented at this meeting has emphasized importance of the peripheral circulation. Study of bone marrow cells in different stroke models revealed early immune activation in these cells. However, the stress of surgery and anesthesia appeared to contribute to some of these responses and these factors need to be considered when interpreting animal stroke model results. Nevertheless, by utilizing a bone marrow chimeric approach, CD36 (an inflammatory mediator that contributes to ischemic worsening due to elevated plasma cholesterol [11]) derived from circulating immune cells was shown to contribute to stroke worsening rather than CD36 derived from the brain. At the clinical level, T cell responses in acute stroke patients demonstrated a TH1 bias, while proteomic analysis of plasma samples from acute ischemic stroke patients revealed the presence of many proteins involved in inflammation and clotting.

Summary:

Current research in the area of stroke and neurodegeneration were presented. Several meeting themes challenged prior concepts showing that vascular stress may precede neurodegeneration, and that microglia possess important pro-survival and protective functions. The peripheral circulation and the status of cell based and regenerative therapies were also reviewed.

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